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The Recognition of Subsidiary Factors in the Ætiology of Infective Diseases

PRESIDENT'S ADDRESS

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INTRODUCTION

ÆTIOLOGY means that part of any special science which deals with causes, and the investigation of infective diseases includes the study of more than one factor. Consideration must be given not to the infective agent alone but also to the relative importance of general hygiene, nutrition, habits, species of animal, breed, sex, age and environmental conditions. Infective diseases apparently never die out and Greenwood *et al.* (1936) wrote of their work on experimental epidemiology in mice: "The disease will never die out. Since in experimental practice a herd may be reduced to a very small number of individuals, it might happen that the disease became extinct. But we think our experience is wide enough to demonstrate that such an event would be a mere accident of small numbers, and that in large herds maintained under the conditions of our study the disease will be perennial." Some mice existed in a state of infection-equilibrium and many immunized survivors were infected and apparently infective for normal mice. This immunization may have been engendered by natural sublethal or latent infection and this is an essential factor in the immunization of any human or animal herd. Although we recognize "epidemic strains" of bacteria which, when introduced into a herd or community exact their toll, it is equally important for us to consider latent infection and those factors which may influence the epidemic characteristics of a strain and are therefore concerned in the ætiology of infective diseases. The following aspects have some bearing on the problem :

(A) The bacterial flora of normal healthy human beings and animals and the mechanism whereby the potential pathogens assume an infective role.

(B) The resistance of individuals as far as we are able to judge by examination of body fluids for antibodies and bactericidal substances.

(C) The different environmental and subsidiary factors which initiate infective diseases and break down any natural immunity.

(A) *The bacterial flora of normal healthy individuals.*—

We are mainly concerned with the potential pathogens harboured by man and animals. During the years 1930–1937, an extensive study of the nasopharyngeal bacterial flora of different groups of persons in London and S.E. England was made by Straker, Hill and Lovell (1939); this was an extension of one made in Manchester a few years earlier (Report, 1930). On the basis of these studies we find that a single examination of any group of adults living in urban communities in a temperate zone would be expected to yield the following frequencies of isolations from the nasopharynx:

Streptococcus pneumoniæ	20–40%
Hæmolytic streptococci	5–15%
Hæmophilus influenzæ	40–80%
Neisseria meningitidis	5–20%

There is a seasonal trend, the general carrier rate tending to fall at any season in association with increasing sunshine and decreasing relative humidity; hæmolytic streptococci show the converse as they were isolated slightly more frequently in hot and dry than in cold damp weather; the meningococcus carrier rate remained relatively steady. The figures suggest that every person examined regularly would have harboured at one time or another within the period of six years *Hæm. influenzæ* and one or other type of the pneumococcus; about three-quarters would have harboured the meningococcus and a hæmolytic streptococcus. Had the examinations been more frequent there is little doubt that each of the pathogenic bacteria under study, and many of the different types within those species, would have been detected at one time or another in each person. The subsidiary report by Rosher and Cole (1939) indicated that whilst *Hæm. influenzæ* was largely confined to the nasopharynx in the summer months, there was a tendency for it to increase the territory it occupied during the late winter and early spring; during this latter period it extended downwards into the trachea and bronchi. There was some suggestion that a similar increase in the area of the respiratory mucosa colonized was associated with certain virus infections, irrespective of the season. There is, thus, a widespread distribution of certain potentially pathogenic bacteria in the absence of overt clinical disease and accessory factors influence their extension and possibly the production of actual infection.

The study of the distribution of potentially pathogenic bacteria in domestic animals has not been so extensive nor so prolonged. In many cases it has been confined to a single examination of groups of animals. An instructive report on the persistence of *Strept. agalactiæ* and its spread in dairy herds has been issued under the direction of the Agricultural Research Council (1944). This organism may be recovered from the milk of cows that show no clinical evidence of mastitis and a high infection rate may be associated with a relatively low incidence of the disease. It was subsequently shown that one single test gave no adequate picture of the distribution of *Strept. agalactiæ* in the milk or on the teats. It was isolated from 38·8% of 16,482 samples of milk and from 23·1% of 5,433 teat swabs but when cattle in nine herds were examined at approximately weekly intervals over periods from two and a half to six months a clearer picture emerged. The proportion of cows in these herds which at one time or another yielded *Strept. agalactiæ* in the milk or on the teats varied from 35·6 to 100% in the former and from 45·7 to 100% in the latter site. The evidence here is that if milk samples and teat swabs are examined from all cattle in such herds

at weekly intervals, the percentage of animals that on one or more occasions are found to harbour *Strept. agalactiæ* in either situation rises rapidly, and that within a few weeks or months may reach or approximate to 100%. Other pathogens capable of causing mastitis have been recovered from normal healthy cattle (Francis, 1941*a*). The percentage in each case was low, ranging from 4 to 9%. This observer isolated *Corynebacterium pyogenes* from 18 of 100 pairs of bovine tonsils which accords with other observations on the ubiquity of this bacterium in certain animal species. It has been isolated from the nose of healthy sheep (Bosworth and Lovell, 1944) and from specimens of mucous membrane of the mouth of cattle (Ochi and Zaizen, 1936). Sporadic cases of infection with this organism occur frequently and support the view that *C. pyogenes* is widely distributed. Summer mastitis, abscess formation and calf pneumonia often develop with no evidence of the introduction of this bacterium from outside and *C. pyogenes* is a common secondary invader in foot and mouth disease (Weinberg *et al.*, 1938), in Pasteurella infections (Lovell and Hughes, 1935), in the lungs of calves born prematurely because of Brucella infection and in calf pneumonia following *Actinobacillus actinoides* infection (Smith, 1921, 1925). A hæmolytic cocco-bacillus, which is allied to the Pasteurella group and credited with causing rhinitis and pneumonia in calves and sheep has also been isolated from the nose and trachea of healthy sheep (Bosworth and Lovell, 1944). Other examples of the distribution of potential pathogens in or on the tissues of healthy animals may be cited. Pneumococci have been isolated from the nasal cavities of guinea-pigs (Neufeld and Etinger-Tulczynska, 1932). *Erysipelothrix rhusiopathæ* is commonly recovered from the tonsils of pigs and recently Taylor (1949) has recovered Johne's bacillus from 37 ileocæcal lymph nodes of 243 cattle.

We can therefore show to our satisfaction that many potential pathogens, and inferentially many others, are harboured by normal healthy men and animals and that one single examination yields an imperfect picture of the true incidence. There should therefore be no hesitation in accepting an epidemiological hypothesis in the absence of cases of overt clinical disease; the causal organism may be more widespread than one series of observations would lead us to expect.

(B) *The resistance of normal individuals to bacterial pathogens.*—

It is difficult to judge the resistance of normal healthy men and animals to a particular infection except by direct experiment. The activity of the phagocytic cells of the body has been well studied and the existence of a unified reticulo-endothelial system is accepted. It is, however, not so easy to estimate the resistance of individuals in the field except by the examination of body fluids and secretions. Specific antibodies play an important, though not the only, part in natural resistance to bacterial infections. The presence of apparently normal antibodies must be correlated with other facts and for this purpose they may be separated into three divisions:

(1) Those bactericidal substances and antibodies which are apparently strictly normal and for which no explanation other than a genetic or developmental one is available.

(2) Those which are probably the result of a stimulus provided by exposure to antigenically allied bacteria or possibly to some other substances chemically or antigenically similar.

(3) Those induced by exposure to the specific bacterium and resulting in a subclinical or latent infection.

(i) Normal serum has a marked bactericidal effect on various organisms, particularly the Gram-negative ones and in many cases it is due to the combined action of complement and a heat-stable factor which does not appear to be related to a specific immune body (Gordon and Hoyle, 1936). Leukins, obtainable from leucocytes

and β-lysins, substances present in serum, are also bactericidal for many strains of bacteria. The bactericidal properties of serum vary according to the species of animal; rabbits, although relatively susceptible to anthrax, exhibit in their sera a bactericidal property for the anthrax bacillus; fowl serum has little effect on this organism and yet the fowl is relatively resistant to the disease. Such facts as these cannot as yet be explained to our satisfaction. Lysozyme is a bactericidal substance present in tears and other secretions, and this suggests that similar substances effective against other organisms may be present in tissues and body secretions.

(2) Surveys of the antibody content of the sera of man or animals living under natural conditions reveal that many samples contain substances that react in the same way as specific agglutinins or antitoxins. Bürgi (1907) found agglutinins for many species of bacteria in the sera of dogs, birds, sheep, horses, goats, cattle and man. Agglutinins against the "H" antigens of 7 different Salmonella were found in the sera of a large number of cattle, sheep, pigs and horses by Lovell (1932) and further examinations were made of the agglutinins against both "H" and "O" suspensions (Lovell, 1934); most of the sera from cattle, pigs, sheep and horses agglutinated many of the suspensions to a low titre whereas, in general, most of the rabbit sera failed to agglutinate any of the suspensions tested. Absorption tests showed the specificity of these agglutinins and there was some evidence of their increased frequency with advancing age. They were probably due to stimulation by bacteria which are normally present in, or on, the tissues of the animals and although not Salmonella bacteria, were in some way antigenically similar. Many examples of the immunological and chemical association of apparently unrelated bacteria are known, e.g. Friedländer's bacillus and pneumococcus Type II, some types of *Pasteurella pseudotuberculosis* and Salmonella, certain strains of *Bact. coli* and Salmonella. Two fæcal strains of *Bact. coli* isolated from the pigs tested stimulated the production of agglutinins for Salmonella in rabbits.

A similar picture emerges from the study made of the agglutinins for *Pfeifferella mallei* in normal horse sera. The median titres obtained with 314 samples were: 1:320 and 1:640 respectively against two different suspensions. All of a few samples from cattle, pigs, goats and rabbits also contained similar agglutinins though to a lower titre. Glanders is a disease of horses, and the history of the horses from which the sera were obtained revealed the extreme improbability of their ever having been in contact with the disease. At the time of the investigation (Lovell, 1935) no case of glanders had occurred in Army horses in this country for well over ten years and the majority of the horses were Army ones obtained from this country or Eire and were less than ten years of age. Furthermore the incidence of glanders in civilian horses had been negligible for some years previous to the investigation. The frequency distribution of these agglutinins, therefore, gave no indication of the incidence of the disease nor of latent infection; the sera of animals which do not normally suffer from glanders, viz. cattle, pigs, goats and rabbits, also possessed agglutinins for *Pf. mallei*. The most reasonable explanation for their presence is that they too were stimulated by the presence of some common substance antigenically related to *Pf. mallei*. Other authors have recorded similar experiences and found no adequate explanation for the presence of these natural agglutinins (Gibson, 1930, 1932; Timmerman, 1930).

Although natural hæmolysins and natural hæmagglutinins develop during growth, and a correlation exists between the increase of natural agglutinins and serum globulin, there is a balance of evidence that the formation of some of the antibodies discussed is due to external stimuli. Their immunological significance is hard to assess and in general they appear to have little or no protective value; it is possible that they may act as the "primary stimulus" rendering the individual more sensitive

to the specific antigen in question. Cows and horses possess agglutinins against *Pf. mallei* in their sera yet their respective susceptibility to glanders is very different. Cattle, pigs, horses and sheep contain agglutinins against Salmonella bacteria in their sera but here again, there is a variability in their susceptibility to Salmonella infections not revealed by serological tests.

(3) There is little doubt that some of the antibodies detected in a survey are due to the stimulus provided by specific infection; in many cases a subclinical one. Some of the antitoxins fall into this class, such as diphtheria and scarlatina antitoxin in man and *C. pyogenes* antitoxin in animals. It is well established that detectable amounts of diphtheria and scarlatina antitoxins are present in about 50% of children during their first few months of life, probably transferred passively from the mother. This resistance is short lived, and after a phase of susceptibility to infection the passive immunity is replaced by an active one caused by exposure to infection. There is thus a gradual process of immunization and after the age of 20 only 10-15% of individuals are Schick or Dick positive (Zingher, 1923, 1924). A survey of the *C. pyogenes* antitoxin content of the sera of different species of animals revealed that the mean antitoxin content of cattle sera was 83·0 "x" units per c.c. and the values obtained with sera of other species were: pigs 84·4, sheep 25·6, pigs 51·5, horses 13·7, man 1·2 and rabbits 0·7 (Lovell, 1939). The higher values and a greater variability occurred in the sera of cattle, sheep, goats and pigs, animals which are naturally and frequently infected with *C. pyogenes*. An intermediate position was occupied by horses, in which *C. pyogenes* infections are almost unknown whilst the sera of rabbits and man, species which are rarely or never attacked, had extremely low values. An association existed in cattle between increasing age and a higher mean and greater variability of antitoxin values; still higher values were observed in animals naturally infected or injected with toxoid. If one links all these facts then one is forced to accept the view that the antitoxin present is specific and that *C. pyogenes* is widely distributed amongst the healthy cattle, pig, sheep and goat population and that infection with this organism is frequently endogenous.

(C) *Environmental and subsidiary factors which initiate infective diseases and break down natural immunity.*—

Immunity is a misleading term and actually means a study of all those factors which disturb a fluctuating equilibrium existing between a parasite and its host. Ryle (1948) asks us to recognize the fact that no disease has a single cause although many diseases have a specific one. Bacteriologists have, in the past, been too absorbed with the specific causes of disease, and clinicians with the alleviation of symptoms; neither has enquired too closely into the actual ætiology of diseases. The examination of body fluids and secretions during life and the study of tissues after death may tell us much of specific causes but little of the factors leading to the morbid changes and to death. Unless we recognize those factors which initiate an infection, thereby giving the specific parasite the upper hand, diagnosis is incomplete and prevention is applied empirically. The laboratory may furnish much but not enough for our needs; field surveys and examinations of groups of animals and men must be made; analyses of the conditions whereby infective diseases arise will indicate future lines of research, first by the formulation of a hypothesis which can then be tested under controlled conditions.

The evidence I have presented concerning the ubiquity of potential pathogens, and inferentially others not yet found, suggests that the onset of many infective processes is conditioned by other factors than mere exposure to infection. Special "epidemic strains" may start an epidemic when they are introduced into a closed or semi-closed community, but how have these special strains acquired the status of "epidemic strains"? Presumably by attacking those individuals which are most susceptible first, and their virulence is then increased by natural passage. The

mechanisms which enable this change of virulence to develop may well be similar to those which convert a latent infection into an overt clinical condition. A study of subsidiary factors may supply an answer to both aspects of medicine. An investigation of the relationship between the distribution of a pathogen, and the specific antibody content of the sera of groups of men and animals, is needed in many cases ; we know little of this relationship in diphtheria in man. The relationship of the distribution of normal agglutinins and the carrier rate of the relevant bacteria, would be more difficult to assess because different stimuli are probably responsible for the agglutinins; in general, normal agglutinins are less specific than the antitoxins.

A large volume of literature on the relationship of nutrition and infection is available but as Gell (1948) has said, it is not easy to demonstrate that mass starvation has been an important factor in the genesis of epidemics of human disease. Famine is not the only feature in such situations, which include overcrowding, insanitary conditions and mass movement of populations. Little is known of the effect of starvation on the bodily defence mechanism; protein starvation may depress the antibody-response to infection, and this may be linked with the inability of young stock to respond well to an antigenic stimulus, especially in ruminants which depend upon colostrum for their protein during their first few days of life. Colostrum supplies a deficiency in protein and probably other substances as well. No widespread epidemics have occurred in man during the last ten years which can be linked with the excessive undernutrition experienced in some areas. Some specific deficiencies are known to predispose to certain infections and this is shown by the relationship existing between a nicotinic-acid-deficient diet and bacterial invasion of the gut wall and the associated lymph glands in pigs (Chick *et al.*, 1938*a*, *b*). On the other hand in some other infections, the strong well-grown individuals are more susceptible to disease; blackleg and anthrax in cattle are more frequent in young well-grown cattle than in the lean ones; foot and mouth disease is more severe in well-grown, well-nourished animals; in fact they are most susceptible when in prime condition and at the prime of life (Edwards, 1937). It may be that the preference viruses have for growing in actively dividing cells may have some bearing on this observation. The nutritional status may play some part in the epidemiology of poliomyelitis as the healthy well-nourished appear to be more frequently attacked than the ill-nourished. Thompson (1949) suggests that the mode of life and personal habits are possibly the deciding factors. Dust-borne infection may be important and that in many sufferers there has been a neglect of personal hygiene; this might explain why the older schoolgirl, the most fastidious member of a community, usually escapes lightly. That nutritional factors influence the response to injections of toxin and toxoids has been shown experimentally in sheep by Mackie *et al.* (1932) and in guinea-pigs by Hartley (1948).

The pharmacological effects of substances in the diet may exert some influence, for example: outbreaks of enterotoxæmia in sheep due to *Clostridium welchii* Type D frequently follow the transfer of a flock from one type of pasture to another, and their return coincides with the cessation of cases of disease. Is there some substance in the diet of the new pasture which facilitates the proliferation of the clostridia? Ferguson (1948) has demonstrated the muscle-inhibitory activity of clover juices and Quin and van der Wath (1938) showed that small doses of cyanide cause complete stasis of ruminal movements in sheep. Various clovers contain cyanogenetic glucosides and one is apt to wonder whether these observations may have some bearing on the onset of enterotoxæmia in sheep.

Certain well-defined factors undoubtedly assist bacteria to establish themselves and proliferate in particular tissues. The influence of tissue damage, soil, calcium salts and proteolytic bacteria in the development of gas gangrene and other clostridial infections is well recognized. The part played by *Fasciola hepatica* in the germination

of spores of *Cl. œdematiens* thus leading to black disease of sheep is also well known. The non-specific non-living agents are difficult to find and to assess and may be associated with a particular habit of man or animals. A deficiency in the diet available may determine such a habit as in lamziekte in cattle and sheep. The toxin of *Cl. botulinum* is the specific cause of this disease but this alone does not explain its ætiology nor provide a method for prevention. A lack of phosphorus in the soil and vegetation leads to a condition of osteomalacia; styfziekte, a stiffness and lameness, follows and in an attempt to overcome this the affected animals have a craving for chewing the bones of the dead; if these are infected with *Cl. botulinum*, a common soil organism, and its toxin, then intoxication occurs with disturbance of deglutition and mastication as well as a more general paralysis. A simple method of prevention presents itself; bone meal or other forms of phosphate are included in the diet and animals cease this habit.

Some interesting lessons can be learned and fresh problems formulated by a study of mastitis in cattle. The disparity between the carrier rate of *Strept. agalactiæ* and cases of contagious mastitis has already been referred to. Hughes (1949) pleads for a recognition of this disparity and for a critical reassessment of many present-day methods of hygiene designed to control the spread of infection. Francis (1941, *b*) considers that the conformation of the teat may assist bacteria to penetrate mammary tissue and that evolutionary and involutionary changes which depend on fluctuations in the concentrations of hormones may also influence the susceptibility of udder tissue to invasion. That skin and teat lesions have some effect has been demonstrated in the infection of cows with *Strept. pyogenes* of human origin (Bendixen and Minett, 1938). The milking machine plays a part in other forms of streptococcal mastitis (Neave, Sloan and Mattick, 1944) and a high incidence has been recorded in herds when the vacuum readings of the milking machine have been too high, or the gauge has been faulty. Mastitis has been produced experimentally by using a high vacuum and the incidence in a herd reduced by a low vacuum. The specific bacteria isolated—*Strept. dysgalactiæ* or *Strept. uberis*—cannot be cited as the whole reason for the mastitis which develops.

The story of staphylococcal mastitis is also far from complete; *Staphylococcus aureus* may cause a mild chronic catarrhal type, a chronic fibrous form or an acute gangrenous inflammation. What factors are responsible for this variation? What is the association between the latter form and parturition? Summer mastitis—the specific cause of which is *C. pyogenes*—occurs most frequently in dry cows and heifers at grass and flies have been held responsible for its spread. This seems unlikely, when we consider the number of cattle which carry the organism. Irritation of udder tissue by flies may aid the migration of the organism to the mammary gland but why does it occur in the non-lactating gland more frequently than in the lactating one? The variable annual incidence, apart from the seasonal incidence, cannot be explained by the variation in the number of immunes and non-immunes at risk. All but 3 of 575 samples of bovine sera examined, contained detectable amounts of *C. pyogenes* antitoxin and this makes such an explanation unlikely. Recourse to field studies and field surveys might indicate profitable lines of research and reveal the actual problem which needs solution. Summer mastitis is still a menace to our dairy herds in spite of our knowledge of the specific cause; its ætiology is obscure.

A specific cystitis and pyelonephritis in cattle is caused by *Corynebacterium renale* and the theories which have been postulated as to why the organism localizes itself in the kidney medulla are, at the moment, the subject of laboratory investigation. There is, however, insufficient knowledge as to why certain cows in a herd suffer and others escape. It has been suggested that there is an association between it and pregnancy; nearly all dairy cattle are in some stage of pregnancy for three-quarters

of each year during their reproductive life. Adequate field studies might tell us whether the onset of the disease is linked with a particular stage of pregnancy and thus lead to an analysis of the factors associated.

Latent virus infection, which is accepted with some viruses, is now credited with a role in the ætiology of certain tumours. A simple working hypothesis of their origin is that the action of a chemical carcinogen prepares cells to accept a latent virus already in existence in the bodies of normal animals (Imp. Cancer Res. Fund, 1949). A similar theory could well be applied and thereafter tested as to the origin of many of the obviously infective diseases.

Many other examples similar to those dealt with exist and one which at the moment is being studied concerns those bacteria which, although non-pathogenic for adults, may cause disease and death in the newly born. Spence (1941) stated that " an organism such as *Bacterium coli* which is relatively innocuous to older children may cause a rapidly fatal illness in a newborn infant and an investigating bacteriologist with fixed ideas of what are pathogenic organisms may be led astray". This outlook is not new in the field of animal pathology, for it has been known for fifty years that *Bact. coli* is capable of killing calves. Similar organisms are now credited with causing diarrhœa in babies (Cass, 1941; Giles and Sangster, 1948; Taylor *et al.*, 1949). In enquiries of this nature, the environment of the young is of prime consideration. The development and nurture of a fœtus are gradual until it is expelled from the uterus, and this sudden change of environment is largely provided for by the transference of a passive immunity to the prevailing bacterial flora, either by the placental vessels or through colostrum, according to the species of animal concerned. Should there be a sudden change of environment of the mother during the latter days of pregnancy, or of the newly born shortly after birth, then the young animal or baby is exposed to a different bacterial flora, which may be harmless to the mother but fraught with danger for the young. The immunity passively transferred may be effective against the bacteria of the previous environment but not necessarily against these now encountered. The diarrhœas of young babies and calves are frequently associated with *Bact. coli*; in lambs it is *Cl. welchii* Type B. In calves and lambs the provision of colostrum, and especially colostrum containing antibodies against the specific and prevailing bacteria, is of paramount importance. Lamb dysentery can be controlled by active immunization of the mother, and the immunity engendered is transferred to the young and this protects it during the period of susceptibility. Owing to the variable antigenicity of *Bact. coli* this method of control is not applicable for "white scours" in calves. Other means have to be sought for, and field studies may indicate the most profitable paths. There is a correlation between the date of calving and the loss of calves; in dairy herds there is a greater loss in the spring, possibly associated with a dietary deficiency in the mother during the winter months preceding parturition (Lovell and Hill, 1940). My colleague Mr. F. W. Withers, who is making a study of the mortality of calves under the direction of the Agricultural Research Council, has permitted me to quote some of his unpublished observations. He finds a correlation between the heavy losses experienced in some dairy herds and an irregularity of non-lactating periods in the cows. A great variability in temperature also appears to favour losses; for example, the month of March is noted for a variation ranging from mild warm weather to cold frosty spells and this is more hazardous for young stock than continued cold weather. Such observations are only possible in the field, and it is important that in these infective conditions, which beset the human population as well as our flocks and herds, such field studies be made. The specific infective agent is one factor in the ætiology of a disease, and a fuller understanding of the ætiology of any condition paves the way for its prevention, often by simpler means than by specific immunization.

SUMMARY

It has been my endeavour to point out how difficult it is to estimate the extent of the carrier rate of pathogenic bacteria in man and animals. In some cases it can be shown by frequent examinations, that certain pathogens are present in or on the tissues of all the individuals examined. It is possible that this state of affairs exists with other pathogenic bacteria, and inferentially with viruses; in many instances our examinations have not been made sufficiently extensive, nor frequently enough, or the technique available is not adequate for the isolation of the bacteria unless they are present in large numbers. With some bacteria this viewpoint has been supported by a serological examination, and we find that all the members of a community acquire, by natural means, a degree of resistance to a specific bacterium or its toxin. In other cases, especially when the serological test employed is the agglutination reaction, the presence of antibodies bears no relationship to the carrier rate. We have then to consider the probability that the stimulus is provided by other bacteria or substances which are antigenically related, and the possession of such antibodies may not mean the enjoyment of any increased specific resistance. When the natural history of some infective diseases is examined we are faced with many questions which at the moment we are unable to answer. By what means are the potential pathogens, which are so commonly found, converted to "epidemic strains" and are then capable of inducing infection in a large number of individuals at risk?

This increase in virulence may be associated with a reduction in the resistance of one individual, thereby enabling the bacteria to proliferate; passage through successive hosts enables it to dominate the bacteriology of a particular herd or area. Is this the mechanism involved in the production of "epidemic strains"? If so, then recognition of those factors which contribute to a reduction in the resistance of the host is called for. There is some evidence to suggest that a similar process is implicated with bacteria which are relatively harmless to adults but assume a pathogenic role in the young. Such problems as these may be solved by a consideration of the subsidiary causes which are involved in infective diseases and these can be determined by careful observations made in the field; that is, by examination of the conditions of life enjoyed by groups of people and herds of animals. The so-called "nutritional status" is not exact enough, as the animal in a good state of health appears to be more prone to some infections than one in a poorer state. The reduction in the major epidemics of the past is likely to be accelerated in the immediate future by the success achieved with modern therapeutic agents and the importance of the specific infective agent will be decreased; more attention will then be paid to the influences of climate, season, diet, habits and other factors in initiating and correspondingly in the prevention of disease. These problems become physiological rather than bacteriological but the physiological problem cannot be enunciated until we have more information of the natural history of diseases. Furthermore our horizon stretches beyond that of preventive medicine; it is the aim of social medicine to provide conditions whereby people may enjoy the fullness of life. This is a positive outlook and may be applied to our animal population too; the well-being of domestic animals is one objective of students of comparative medicine, as animals which are in excellent health and condition provide the community with good food and other necessities. Such a state may be achieved not only by the application of discoveries made in laboratories but by paying adequate attention to observations of the clinician and field worker.

> "Then shall two be in the field; the one shall be taken, and the other left. Two women shall be grinding in the mill ; the one shall be taken, and the other left."—(Matt. xxiv, 40-41.)

This occurs in medicine to-day and one day the reasons may be revealed to us.

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Section of Physical Medicine

President—H. A. BURT, M.B., B.Chir., M.R.C.P.

[*October* 12, 1949]

Cortisone (Compound E) and Adrenocorticotrophic Hormone in Rheumatoid Arthritis

By OSWALD SAVAGE, O.B.E., M.R.C.P.

WITH some fifty other physicians from all over the world I was privileged to see the work on Cortisone at the Mayo Clinic in June 1949, and it so happened that by chance I was called out by Dr. Hench to examine one of the two cases we saw both before and after treatment. There is no doubt in my mind, or I should imagine in the mind of anyone else who was there, of the remarkable changes effected by this drug in rheumatoid arthritis.

As one would expect from such a team as Hench, Kendall, Slocumb and Polley (1949) the work has been most carefully checked and controlled, and the cases which we saw were suffering from severe active rheumatoid arthritis of some standing. We saw two cases before treatment, one with Cortisone and one with A.C.T.H., and the change effected by only two and a half days' treatment was extraordinary. One woman of 55 years had suffered for three years; she could hardly walk and it took her two hours before she could do her hair in the morning. Her sedimentation rate was 67 and she was taking 60 grains aspirin per day. After even such a short period of treatment as two and a half days she was free from pain and we saw her walk normally. She felt a sudden improvement nine hours after the first injection—as she put it "I feel a load taken off"; another remark she made was "I can do anything right away".

The history of the work is a fascinating one, for during the war it was rumoured that the German pilots were being given injections of suprarenal extract to increase their fighting efficiency and so momentum was given to work proceeding on the cortical substances.

For many years Hench (1949) has been studying the reversibility of rheumatoid arthritis and eventually discarded the microbic theory, as he said in his Heberden Oration in this country last year, and turning to the biochemical possibilities he concluded that the "antirheumatic substance X", as he called it, might be an adrenal hormone.

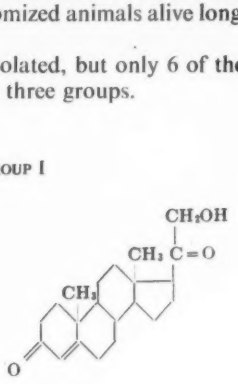
If we are to understand the work done on Cortisone we must study the present-day work on the adrenal steroids.

All this work is comparatively recent and dates from the 1930's for before that time it was impossible to keep adrenalectomized animals alive long enough to examine the effects of giving cortical substances.

So far 28 adrenal steroids have been isolated, but only 6 of them are active as far as is known. These 6 can be divided into three groups.

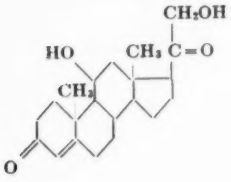
GROUP I

Desoxycorticosterone

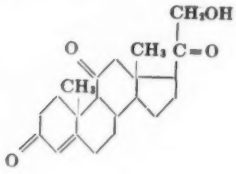


GROUP II

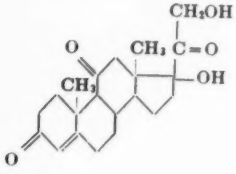
Corticosterone (Compound B)



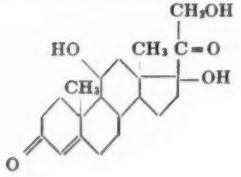
Dehydrocorticosterone (Compound A)



17-Hydroxy-11-dehydrocorticosterone (Compound E)

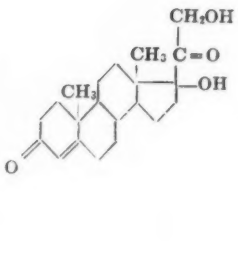


17-Hydroxycorticosterone (Compound F)



GROUP III

17-Hydroxy-11-desoxycorticosterone (Compound S)



Amorphous fraction

The first contains desoxycorticosterone alone. The second contains corticosterone, dehydrocorticosterone, 17-hydroxy-11-dehydrocorticosterone and 17-hydroxycorticosterone. You will see these are all oxygenated at the 11 position and because of this are called 11 oxysteroids. It is this group with which we are principally concerned because it contains Compound E now called Cortisone. This group is also referred to as the glycocorticoids because they are chiefly concerned with carbohydrate metabolism; sometimes they are just called corticoids. The third group is composed of what is left over. There is 17-hydroxy-11-desoxycorticosterone or Compound S which has little effect on carbohydrate metabolism and when the crystalline fractions have been extracted there remains a highly active residue called the amorphous fraction which has been little studied.

Desoxycorticosterone or its acetate D.O.C.A. has been the most studied of these active steroids, as so far it is the only one for which a cheap method of synthetic production has been available and it has been used chiefly for Addison's disease. In 1937 Steiger and Reichstein announced its synthetic preparation from stigmasterol and a little later Reichstein and Van Euw (1938) recovered it from the adrenal cortex. Desoxycorticosterone causes a marked retention of sodium, chloride and water and increases the excretion of potassium and phosphorus; however, it exercises hardly any effect on carbohydrate metabolism. In Addison's disease it will restore the blood electrolyte pattern to normal and elevate the blood-pressure and is life-saving in Addisonian crises. Its continued use can result in œdema and heart failure.

Our group, the 11-oxysteroids containing corticosterone, dehydrocorticosterone, 17-hydroxy-11-dehydrocorticosterone (Cortisone), 17-hydroxycorticosterone, are concerned chiefly with carbohydrate metabolism.

As early as 1930 Britton enunciated the theory that the "prepotent function" of the adrenal cortex was to regulate carbohydrate metabolism. He observed that the adrenalectomized animals developed acute hypoglycæmia and low glycogen levels and that when normal fasted animals were given large doses of cortical extracts there was an increase in blood sugar and in both liver and muscle glycogen. These views were met with misgiving but they now fit into the picture of established fact.

In 1936 Mason, Myers and Kendall, and in 1937 de Fremery and his co-workers isolated corticosterone, now called Compound B, and dehydrocorticosterone, now called Compound A, both extracts of the adrenal cortex, in crystalline form. They found they could maintain adrenalectomized animals in good condition by giving these substances.

Kendall (1941) at the Mayo Clinic isolated 17-hydroxy-11-dehydrocorticosterone from the adrenal cortex and called it Compound E; a few weeks later Pfiffner and Kamm (1942) in Switzerland isolated the same compound and called it F. This caused some confusion and the substance is now known as Cortisone. Another compound called S has also been isolated and has the chemical name of 17-hydroxy-11-desoxycorticosterone but having no oxygen at C 11 it has no effect on carbohydrate metabolism.

The four compounds, A, B, E and F have a marked effect on carbohydrate metabolism and E, or Cortisone, is by far the most active in this respect. Compound F is so unstable it is difficult to study. Thorn has divided this group into Compounds A and B, the 11-oxysteroids, and Compounds E and F, the 11-17-oxysteroids, which have an OH group at the 17-position.

They cause an increase in the blood glucose levels and the liver glycogen stores. They cause an increased conversion of protein to carbohydrate and also an increase in the renal clearance of uric acid, resulting in the excretion of large quantities of urates both in normal subjects and patients with gout.

Compounds E and F, the 11-17-oxysteroids, have an effect on the lymphoid tissue which is shown by the decrease in the number of circulating eosinophils and also lymphocytes.

The other substance which has been tried is A.C.T.H., the pituitary adrenocorticotrophic hormone. It has recently become available in sufficient quantities to study its effect on the secretion of adrenal steroids in man. It causes a profound fall in circulating eosinophils and a rise in the urinary uric acid excretion. It causes sodium and chloride retention, a rise in blood sugar level, an increase in the excretion of 17-ketosteroids and a rise in the level of circulating 11-oxysteroids. In fact in man it causes increased secretion of adrenal steroids, giving the effects observed with the crystalline adrenal steroid preparation and of adrenal hormone therapy. In short, it reproduces the effects of Cortisone therapy in rheumatoid arthritis.

Now for the clinical effect of Cortisone in more detail. The clinical improvement may start after only four hours but it is usually felt in the first day or two. The first effect is on the stiffness and the patients say they feel as if something had been unlocked from their limbs. They lose their pain remarkably quickly and joints which were tender on firm pressure become painless. The swelling does not, of course, go so quickly, but I understand that mildly contracted joints have straightened out on Cortisone though I did not see this myself.

These patients get a remarkable euphoria and very often lie awake for the first night or two, free from pain and excitedly planning a future free from arthritis. After this phase they usually fall into a sleep of exhaustion. They acquire a ravenous appetite and eat so much that later they may have to be dieted to avoid obesity.

At the International Congress of Rheumatic Diseases in New York last June Dr. Hench showed a film of a patient whom we later met at the Clinic. His joints were tender to firm pressure and he could hardly get up and down steps. After nine days' treatment the film showed he had lost his tenderness and could go up and down the steps quite normally. He offered to run for the film outside the hospital but as there was snow on the ground he was only allowed to do so in the studio.

What about the objective tests? The sedimentation rate comes down to normal but is not so rapid as the remarkable clinical improvement. As Dr. Hench puts it "the B.S.R. and the symptoms are travelling in the same train but not in the same carriage".

The anæmia of rheumatoid arthritis responds to Cortisone alone and no iron or other medication is required. The albumin-globulin ratio reverts to normal.

It was perhaps a stroke of genius which led Hench to try the first case on what might be considered a tremendous dosage for hormone therapy, because if he had not done so he might have missed the bus entirely. Cortisone does not work except in large doses and the cases which we saw which responded so remarkably had 300 mg. the first day and 100 mg. subsequently. It is given by injection and the drug is so expensive and precious that every precaution is taken to see that none is wasted.

With A.C.T.H. the dosage is smaller but given more frequently and the patient we saw treated had 50 mg. t.d.s. the first day and 25 mg. t.d.s. the second day.

I believe the side-effects have been rather over-emphasized but as Hench says: "This stuff is dynamite" and it is extremely important that they should be noted and publicized, because, when this drug becomes available it should not be used except under the most carefully controlled conditions in hospital.

The Side-effects

These can be discussed under two headings: (1) Those due to pituitary upset; (2) Those due to the upset of the electrolyte balance.

The pituitary upset gives rise to Cushing-like changes which are manifested by a rounding of the facial contours, hirsuties with a growth of hair on the face, purple

striæ, comedones, amenorrhœa and depression. These occur usually after about two weeks but in one case began earlier in treatment. In another case we saw that well-marked purple striæ had been produced across the buttocks.

The upset in the electrolyte balance may give rise to œdema due to the sodium chloride retention and to alkalosis.

A.C.T.H. has given rise to severe headache and vomiting on occasion.

Cortisone and A.C.T.H. have to be continued indefinitely; unfortunately directly the drug is stopped the symptoms return within a few days and the sedimentation rate rises again. It must be remembered that only severe cases have been treated so far but it does look as if treatment has to be continued.

The difficulties of production are immense and 39 long and difficult steps have to be passed before a minute yield of Cortisone is gained from desoxycholic acid. Apparently with the finding of *Strophanthus sarmentosus* this number has been reduced to 17 but the chemists still face a most difficult procedure. Owing to these difficulties, only 17 cases had been treated by June 1949 at the Mayo Clinic though some of these had been under treatment and control periods for over six months. It may be said that this is too few to establish the remarkable claims made, but all except one had responded dramatically.

One of the most remarkable moments at the International Congress on Rheumatism was when, after Dr. Hench and Dr. Kendall had delivered their papers on Cortisone, five physicians who were known to be extremely critical of any claims for the successful treatment of rheumatoid arthritis, who had been invited by the Mayo Clinic and each given sufficient to treat one case under his own control, came on to the platform and confirmed the remarkable effects of this drug in their own cases.

Apart from applauding the authors and their brilliant piece of research we should consider what advance has been made in the study of rheumatic diseases.

To my mind there are two main points of progress even before the drugs are available to study on our own cases. Point 1 is that it has been shown for the first time that the progress of rheumatoid arthritis is rapidly reversible by a drug. Dr. Hench has pointed out that the condition is reversible in pregnancy and sometimes in jaundice and now a drug has been found that can do the same thing. Point 2 is, I believe, equally important: we have a yardstick to evaluate treatment. The trouble with the treatment of rheumatoid arthritis has been that there are so many forms that improve the patient up to a point. Some are better than others and I believe myself that gold is one of the good ones but it is almost impossible to demonstrate that any one of ten or more treatments is better than another.

The rapid and dramatic improvement with Cortisone and A.C.T.H. is most striking compared with anything we have seen before, or any other present-day treatment of rheumatoid arthritis.

I hope I have made it quite clear in this short talk that all the credit for this work should go to the research team at the Mayo Clinic, Drs. Hench, Kendall, Slocumb and Polley.

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Dr. Raymond Greene: *Some Endocrinological Aspects of Rheumatoid Arthritis.*

The realization of the rôle of the adrenal cortex in the ætiology of rheumatoid arthritis seems to have come with shock-like suddenness to the profession at large. In fact, however, many workers on both sides of the Atlantic have been studying the question for some years (e.g. Coke, 1945, and Bassi, 1946). Much of this work is doubtless unfinished and therefore still unpublished, but as early as 1944 Selye and others claimed to have produced arthritis in nephrectomized rats with D.C.A. combined with a high salt intake. His results were disputed by Harrison in 1946, but whatever may be the ultimate judgment on Selye's results his paper focused further attention upon the adrenal cortex, an attention which became still more intense with the publication of his monograph on the General Adaptation Syndrome in 1946.

My own interest in the subject began some twelve years ago. Whereas Hench and his colleagues reached their inspired guess by a study of two conditions (jaundice and pregnancy) which alike may cause a temporary remission of the disease, I approached the problem by a different path, preferring rather to seek the common factor in a number of apparently distinct conditions often associated with the onset of the disease—puberty, lactation, the climacteric, psychological strain, infection and perhaps thyrotoxicosis. The hypothalamic-endocrine system appeared to be a possible connecting link between these apparently various exciting causes, and, within this system, the adrenal cortex the most likely area to explore.

In April 1944 a patient was admitted under my care to Tindal House Emergency Hospital, Aylesbury, suffering from extremely severe rheumatoid arthritis, his condition strongly resembling that of the next patient to be described. I treated him with Eucortone, D.C.A., and anterior pituitary corticotrophic hormone without producing any improvement. Despite later recourse to all orthodox methods he died some months later. In the light of the Mayo Clinic report it seems likely that the sample of corticotrophin was inactive. The difficulty of obtaining corticotrophin caused me for some time to concentrate my attention on the possible effects of whole adrenal extracts and of D.C.A., both of which I found to be ineffective. These are, I gather, under trial in the U.S.A. I can assure workers there that their efforts are vain.

On November 25, 1946, a labourer aged 28 was admitted to the Metropolitan Hospital in an apparently moribund condition. In addition to rheumatoid arthritis of a greater severity than I had previously seen, he had severe pemphigus.

[Here Dr. Raymond Greene described in detail the history, investigations and the general measures of treatment given.]

In addition to these general measures, adopted of necessity and in the full realization that they seriously vitiated the scientific value of the experiment, I set up an intravenous procaine drip, a course which demands some explanation.

I had abandoned the use of whole cortical extracts and of D.C.A. as useless and the difficulty of obtaining corticotrophin in quantity had caused me to seek other methods of stimulating the adrenal cortex. It appeared possible (Ungar, 1944) that procaine, perhaps acting by way of the anterior pituitary, might be such a substance. This point will be the subject of a separate communication.

Within two days of beginning treatment with procaine improvement was noticeable. His joints became less painful and could be moved gently through a few degrees without pain. His morale, which had sunk to a very low ebb, improved. The pemphigus ceased to spread and the E.S.R. dropped from 90 mm. to 40, and at the end of a fortnight of treatment to 16 mm. Apart from this last rather unreliable criterion it might be suggested that improvement was due to the anæsthetic properties of procaine, a possibility which cannot be dismissed. Against such a supposition is the fact that improvement continued (though more slowly) after the cessation of treatment. By the end of December 1946 he could eat solid food and the pemphigus was clearing rapidly. In January the E.S.R. was 10 mm. and his joints were free from pain. He got up on February 8, 1947, when he was weighed for the first time. He weighed 7 st. 2 lb. (45·4 kilos) and it was thought that he had put on about two stones (12·7 k.).

Improvement continued, but very slowly, and in early March slight deterioration began, though the E.S.R. was still normal. By this time I had obtained some corticotrophin through the kindness of Dr. A. Macbeth of Organon. A course of daily intramuscular injections was begun on March 6 and continued until March 23. The daily dose was only 2–3 mg. A great improvement occurred during treatment but was not afterwards maintained. In May his E.S.R. was found to be 45 mm. On May 6 procaine injections were started again and continued until June 9. The E.S.R. dropped to 9 mm.

From that time functional improvement continued very slowly, but the disease remained inactive and he was finally discharged on December 15, 1947, with no disability other than a painless deformity of his hands. He has remained well ever since ; he is, as far as I have been able to determine, the first patient to be treated successfully for rheumatoid arthritis with corticotrophin. [Dr. Raymond Greene then demonstrated the case.]

His continued good health requires explanation. Hench's patients need continued treatment. The most likely explanation seems to be that at some time during 1947 a spontaneous remission was "due." Those who saw him on his admission are convinced that he would not, without the treatment he received, have lived to enjoy that remission. Nevertheless I remain loth to attach much significance to a "cure" produced by so many concurrent methods of treatment.

One other patient was treated successfully with corticotrophin in March 1947. The difficulty of obtaining supplies then caused me to concentrate my attention on other possible methods of producing increased adrenal cortical activity and in particular on the effects of adrenaline (Vogt, 1944), iso-propyl-noradrenaline, the antihistamine drugs, ascorbic acid, nupercaine, and procaine, substances which have an inhibitory effect on histamine release (Ungar, 1944). It is interesting to note at this point that procaine hydrochloride is the hydrochloride of the base prepared by the interaction of chloroethyldiethylamine and sodium para-aminobenzoate. Benadryl is chemically a closely allied substance. I am not ready yet to make any statement on the majority of these substances, but it may be of interest to report briefly on 12 patients, all of whom have received procaine by slow intravenous infusion.

Of 3 who received under 10 grammes, 1 showed a moderate improvement and 2 no improvement.

Of 4 who received between 10 and 20 grammes, 2 were improved to the extent of a temporary cure, 1 was moderately improved, and 1 not improved.

Of 5 who received over 20 grammes, improvement amounting to temporary cure occurred in 2, moderate improvement in 2 and slight improvement in 1.

This improvement may have been the result of the local anæsthetic action of procaine or of some other mechanism entirely unrelated to the adrenal cortex. Moreover we cannot regard the use of intravenous procaine as a serious advance in treatment. It shares with Cortisone and corticotrophin, which are far more effective, the disadvantages of affording usually only temporary relief and is, in addition, impracticable except in hospital. If, however, its effects are indeed mediated through the adrenal cortex, as Ungar's experimental work suggests, the clinical improvement produced is of theoretical interest in that it draws attention to the possibility of attaining our ends by means less difficult in practice than the use of Cortisone or corticotrophin.

My reason for suggesting that the effects of procaine are not dependent on its local anæsthetic effect now needs explanation.

It has long been a matter of interest to those concerned with both rheumatology and endocrinology that in two types of rheumatoid arthritis, Still's disease and Felty's syndrome, the joint changes are associated with enlargement of the spleen. Since 1932, a number of reports have occurred of improvement in rheumatoid arthritis after splenectomy, including one by Bach and Savage in 1940, and by Bach in 1946. In this latter report Bach drew attention to the rise in blood cholesterol in starvation, pregnancy and jaundice and after splenectomy, and pointed out that cholesterol may well be the mother substance of the sterols of the adrenal cortex. The results of splenectomy are so unreliable (Coburn and Pauli, 1935) that the operation has been abandoned. Nevertheless the hint may be worth taking.

In 1945, Ungar claimed to have demonstrated the presence of two substances in the serum of traumatized guinea-pigs. One, which he afterwards called splenin A, decreases bleeding time and the other, which he called splenin B, increases it. Splenin A increases capillary resistance and inhibits histamine release. He claimed that the release of splenin A is dependent upon a chain of events beginning with trauma, which produces an increase in the output of corticotrophin from the anterior pituitary, which causes an increase in the activity of the adrenal cortex, which in turn causes the output of splenin A from the spleen. He suggested that an increase in splenin A might be part of the alarm reaction of Selye, and stated that splenin A is present in normal human blood, whereas splenin B is not. His experiments have not yet been confirmed.

Selye having already hinted at the possibility of rheumatoid arthritis being an example of a failure of his alarm reaction (a suggestion made probable by the great variety of traumata which may apparently initiate the disease), it occurred to me that it would be worth while to determine whether these substances were present in the blood of patients suffering from rheumatoid arthritis. I therefore supplied Dr. Ungar with six specimens of blood from patients suffering from various disorders unknown to him. He reported a complete absence of splenin A and the presence of splenin B in the 2 patients mentioned above who were afterwards treated with corticotrophin. After corticotrophic therapy, splenin B disappeared from the blood and splenin A was found. The other four bloods contained normal amounts of splenin A and no splenin B.

Ungar has since reported the presence of splenin B in the blood of patients with scurvy, various hæmorrhagic conditions, acute rheumatism and thyroid deficiency. Miss Vaughan-Morgan, who was taught the technique by Dr. Ungar, working under my direction at the Royal Northern Hospital, has found it in some cases of thyrotoxicosis.

Ungar and I then proceeded to look for splenin A and B in the blood of a number of patients suffering from active rheumatoid arthritis, some of them under my care and some under that of Dr. Harry Coke.

Since Dr. Ungar left for Canada, his work has been carried on by Miss Vaughan-Morgan at the Royal Northern Hospital. Since the results reported to me by Dr. Ungar and by Miss Vaughan-Morgan are not entirely in agreement, I review their results in separate tables. I have omitted actual figures of units of splenin A and B, because, though Ungar considered his test to be quantitative as well as qualitative, Miss Vaughan-Morgan and I came early to the conclusion that the test in our hands had only a qualitative significance.

(1) Tests Performed by Dr. G. Ungar on Patients Examined Clinically by R. G. or by Dr. Coke

Diagnosis	Number of cases	Splenin A Present	Splenin A Absent	Splenin B Present	Splenin B Absent
Healthy control	1	1	0	0	1
Rheumatoid arthritis, active	10	2	8	8	2
Rheumatoid arthritis, inactive	3	3	0	0	3
Spondylitis, active	1	0	1	1	0
Spondylitis, inactive	1	0	1	0	1
Non-articular rheumatism	9	3	6	3	6
Osteo-arthritis	1	0	1	0	1
Prolapsed disc	1	1	0	0	1
Active infective arthritis	1	1	0	0	1

Ungar (1947) has reported that in 12 healthy persons splenin A was constantly present and splenin B constantly absent. Bergel (1947) (personal communication) states that in 33 normal controls, splenin A was constantly present and B absent. Miss Vaughan-Morgan has recently embarked on a series of tests of healthy persons as a further confirmation.

(2) Tests Performed by Miss Vaughan-Morgan on Patients Examined by R. G. Before Treatment

Diagnosis	Number of cases	Splenin A Present	Splenin A Absent	Splenin B Present	Splenin B Absent
Rheumatoid arthritis, active	15	3	12	15	0
Thyrotoxicosis, before operation	9	4	5	6	3

In 3 cases tested also after operation, A was absent before and after, and B was increased.

Combining the series it is seen that of 25 cases of clinically active rheumatoid arthritis, splenin B was present in the blood of all but 2. Splenin A was present also in that of 5 only. The blood of 3 cases of inactive rheumatoid arthritis contained splenin A but no splenin B.

No conclusions can be drawn from the results in other disorders, but Ungar, Vaughan-Morgan and Bergel all found A present in and B absent from the blood of all healthy controls.

In the blood of the 2 patients with rheumatoid arthritis treated with corticotrophin, splenin A was absent and splenin B present before treatment; but splenin A present and B absent afterwards. The results were less clear-cut in the patients treated with procaine.

Dividing the cases as before, according to total dosage received, the following results were recorded:

Case No.	Dose	Splenin A Before	Splenin A After	Splenin B Before	Splenin B After	Result
I	10 grm.	+	−	+	+	No improvement
II		−	−	+	−	Moderate improvement
III		−	−	+	+	No improvement
IV	10 to 20 grm.	——Results of tests lost——				Great improvement
V		+		+		Great improvement
VI		+	+	+	−	Moderate improvement
VII		−	−	+	+	No improvement
VIII	Over 20 grm.	−	+	+	−	Slight improvement
IX		Tests not performed				Great improvement
X		−	+	+	−	Great improvement
XI		Tests not performed				Moderate improvement
XII		−	+	+	−	Moderate improvement

From this it will be seen that the 3 cases of rheumatoid arthritis which failed to improve all showed splenin B in the blood before and after treatment. In these 3 splenin A either disappeared or was never present.

Of those 9 cases which improved, all those tested showed the disappearance of splenin B during treatment and in 3 cases the reappearance of splenin A, previously absent.

Discussion

I fully realize that these findings are incomplete. My excuse for their premature publication is my belief that the time has come for all those who have in their possession any information which may possibly be relevant to the issue to place it at the disposal of workers on the subject of the endocrine aspects of rheumatoid arthritis. Only one definite fact emerges—that the blood of patients with rheumatoid arthritis usually contains a substance which increases the bleeding time of guinea-pigs and that this substance is usually absent after the treatment of the patients with corticotrophin or with large intravenous doses of procaine.

If Ungar's work on the spleen can be confirmed, my results afford a prima facie case for further work on the part which may be played by the spleen in the ætiology of rheumatoid arthritis.

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Dr. Max Reiss : As far as I am aware, Hemphill and Reiss were in 1942 the first to treat patients with biologically standardized and purified adrenocorticotrophic hormone. The patients were a group suffering from involutional melancholia. Apart from the mental improvement a skin phenomenon was described which might be of interest for this meeting. " In every case the skin soon began to look and feel to the touch more supple and thicker . . . the hair of the head regained its lustre, losing some of its dry brittle quality." Later we saw that the skin became more elastic and its electrical conductivity decreased. Excretion of 17-ketosteroids was shown to be increased. We used only a dose equivalent to 1·5 – 3 mg. of one of the present American preparations. Their dose is many times higher than the hormone produced physiologically. The pharmacological action of such doses, apart from the beneficial effects as in rheumatism, can produce diabetic changes, alterations in the blood pressure and so on. These high doses will ultimately be used, as Thorn and his co-workers suggest, to test the reaction capacity of a patient's adrenal cortex only. Physicians dealing with rheumatism will have an opportunity to study biochemical changes involved in the rheumatic symptom complex. But therapeutic measures will be designed to increase endogenous production of corticotrophic hormone.

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Dr. M. G. Good: I am very sorry to pour cold water on the hopes raised by the speaker; in the official report of the New York Congress, Hench *et al.* claimed no cure, not even a treatment but an investigation into a treatment of rheumatoid arthritis. The evidence available to date on a relatively small number of cases treated for a short time shows that daily injection of 100 mg. of Cortisone relieves the pain completely and thus enables movement in the diseased joints. However, this is due to a *temporary* relief of pain, and after cessation of the injection the patient is as bad as before, including a raised E.S.R. Hench himself called Cortisone "dynamite", which obviously cannot be given for months and years.

The hypothesis that a deficiency of Cortisone is *the* cause of rheumatoid arthritis is at variance with clinical observations. In Addison's disease no rheumatoid arthritis or rheumatism have been observed !

On the other hand it is necessary to point out the very close chemical relation between the structural formulas of Cortisone and other potent natural hormones, like sexual hormones and D-vitamin. Daily injections of enormous and unphysiological doses of Cortisone must needs produce unpleasant side-effects such as virilism in women, painful gynæcomastia in men. Among others the danger of malignant new growths cannot be excluded at present.

In contrast to the "dynamite" Cortisone I have been obtaining in the last twelve months excellent therapeutic results—I might even say a cure in rheumatoid arthritis (about 80–90 cases) by injection of procaine into specific "myalgic spots". [The cases were demonstrated at the meeting of the Clinical Section on October 14, 1949.]

Dr. Francis Bach : Compound E or Cortisone is not, in my opinion, and never will be, the treatment for rheumatoid arthritis. It is interesting to consider how, in the last twenty years, we who are interested in the study of rheumatism have seen, and even taken part in, the early phase of "focal infection", then that of focal conflict (psychosomatic studies) and now have returned to Sydenham's holistic approach.

The fundamental and dramatic work of Kendall, Hench and Thorn which we saw in America has advanced our understanding of man's endocrine system, and, in particular, the mechanism of the hypothalamic, anterior pituitary adrenotrophic, thyrotrophic, gonadotrophic splenic relationship.

I would mention two points of possible interest in this connexion. In those rheumatic patients to whom Dr. Greene referred who, some years ago, at my instigation, had their spleens removed, the disease has remained clinically "inactive". In one patient in whom the clinical picture was first that of an acute thyrotoxicosis, apparently with a normal basal metabolic rate, thyroidectomy was performed. This was followed immediately by the onset of an acute rheumatoid type of arthritis, with swelling of the joints and gross muscle spasm. There was no response to any of the orthodox methods of treatment. Then, some five years ago, splenectomy was performed and complete relief of muscle spasm and the disappearance of all clinical and laboratory signs of activity followed. Now the patient is undergoing a series of operations for joint reconstruction by Mr. Timbrell Fisher, the orthopædic surgeon.

Certainly we have much to learn about the adrenal, thyroid and spleen in their relationship to rheumatoid arthritis.

Dr. M. H. Lessof: Could Dr. Greene say how hepatitis is thought to cause remissions in cases of rheumatoid arthritis? Is there an analogy with cirrhosis or other liver disease, in which the liver's failure to destroy hormones may cause gynæcomastia (Davies, J. N. P. (1949) *Brit. Med. J.* (ii), 676) or fluid retention (Ralli, E. P., *et al.* (1945) *J. Clin. Invest.*, **24**, 316).

Dr. Raymond Greene: So far as I am aware there is no known explanation.

Section of Obstetrics and Gynæcology

President—LESLIE WILLIAMS, M.D., M.S., F.R.C.S., F.R.C.O.G.

[*October* 21, 1949]

DISCUSSION: WHITHER ANTENATAL CARE?

Mr. Aleck Bourne described three phases in the history of the development of antenatal care, and paid tribute to the pioneer work of Pinard and Ballantyne.

He then proceeded as follows:

The fourth phase saw the gradual development of examination of the mother for the presentation, contracted pelvis, and prevention of toxæmia by repeated testing of the urine for albumin. For years these details absorbed the whole attention of the obstetrician, and in many clinics they are still the chief and even the only interest of those in charge.

At first the woman was asked to attend the clinic once or perhaps twice during the last weeks of pregnancy, because the emphasis was laid upon "structure", by which I mean the measurement of the pelvis and the size and presentation of the baby. Testing urine for albumin was the only example of the care of "function".

In these early days it was uncommon to examine the woman at the beginning of pregnancy, to consider her general health, personality and social surroundings. The almost exclusive attention to structure led us to interfere with pregnancy in the form of an enormous amount of surgical induction of labour and an ever-increasing practice of unnecessary Cæsarean section. We were obsessed by the risk of difficult labour due to contracted pelvis diagnosed by minor reductions of the external measurements. If, for any reason, the head was high and could not easily be pushed down through the brim, the woman was in danger of induction of labour. Herman, in his edition of 1910 of that truly remarkable book "Difficult Labour" actually gave a table correlating the length of the true conjugate diameter of the brim with the correct week for induction.

For each quarter of an inch reduction of the true conjugate he gave the correct date for induction of labour, beginning with the 28th week for a diameter of 2¾ inches. He admitted that the actual date should be confirmed by the possibility of pushing the head down because of variations of the size of the child, but he makes no mention of the importance of good uterine contractions.

Interference during the last month of pregnancy was practised on such a scale at Queen Charlotte's Hospital—and most others—that Watts Eden was able to publish a paper showing that the risk to the baby of premature delivery down to the 36th week was so small that induction could be performed without anxiety.

I have looked up the Queen Charlotte's Reports and find that the percentages of induction of premature labour of the total admissions were as follows:

	%		%
1908 —	2·3	1920 —	5·3
1910 —	4·0	1921 —	7·4
1912 —	2·5	1922 —	6·0
1913 —	5·0	1923 —	6·6

In the peak year of 1921 no less than one in every thirteen women admitted had their labour induced. In short, the consideration of labour up to very recent times was entirely mechanistic. There seemed to be no idea of the paramount part played by uterine function in meeting the minor difficulties due to certain abnormalities of structure.

During the years after 1930 the maternal death rate was still rising and there seemed to be little achievement as a result of fifteen and more years of antenatal care.

From 1928 the mortality had been steadily rising until it reached 4·41 per 1,000 live births, the highest figure since 1894. And this in spite of the better training of midwives and students, backed by publications from the Ministry, notably by Dame Janet Campbell. It is not surprising that critics appeared during the 1930s drawing attention to the disappointing

results and asking what was lacking in the whole system of antenatal care. It is necessary, however, to point out here that much of the mortality of mothers was not due only to failure of the purpose of antenatal care but in a large part to the mismanagement of labour. Though the standard of antenatal care may be very high, the woman may lose her life if she is savagely handled during labour.

One such article was published by Mr. A. J. Wrigley (*Brit. med. J.*, 1934, i, 891). He pointed out various defects, but the one which I wish to underline was the mechanistic approach to pregnancy and labour which led to so much unnecessary interference by induction of premature labour and Cæsarean section. Gradually it was realized that external measurements of the pelvis were useless, but the mechanists gained a further encouragement by the more exact estimation of the size and shape of the pelvis by X-ray pelvimetry. If the pelvic diameters could be measured to within half a centimetre and the diagnosis of gynæcoid, android and other shapes could be seen so clearly on the three main films it seemed that the prognosis of labour could be made with equal assurance. On radiological evidence alone many radiologists append an opinion on the prognosis of labour. If we have due regard for the part played by contraction and relaxation of the uterus in labour, we must realize that in the large group of minor deviations from what is arbitrarily recognized as the normal, it is clear that labour cannot be predicted unless we can also foresee something of function.

Throughout the whole range of medicine we are liable to restrict the normal state within too narrow limits. This was well described in a recently published lecture by Professor John Ryle. In obstetrics we are perhaps more guilty of these arbitrary standards than our colleagues. An outstanding example is the diagnosis of pelvic contraction by minor reductions of X-ray measurements. It is true that small reductions may be related to difficult labour if the uterine contractions are continuously feeble, but it is also probable that such a feebly acting uterus would find an equal difficulty if the pelvis were larger than the standard normal.

There are few complications of labour, even including placenta prævia, heart disease, eclampsia and many others, which do not lose something of their potential danger if the uterus acts strongly. If the pelvis is slightly contracted an efficient uterine function can flex and mould the head, dilate the cervix, rotate a posterior occiput, exert pressure on a low placental site, cut short the number of eclamptic fits, and overcome perineal resistance. In all these conditions the dangers are greatly reduced, indeed, labour will probably terminate without anxiety, but if on the other hand contractions are feeble and inconsequent, all these and other handicaps will involve both mother and child in peril.

It is unnecessary to define what is meant by good uterine function because all of us who have attended labour know well what it is. But if function is of paramount importance, can we, during the antenatal period, predict its quality or do anything to ensure it after labour begins? I think we can in most cases. Though speaking without anything like full knowledge of the physiology of the uterus in labour, I would claim that its action depends primarily on the personality of the woman, her emotional attitude to pregnancy and labour and the behaviour of her nearest relations. Secondly, it is dependent upon her clinical type. It is difficult to state briefly what I mean by these words. Let me illustrate. A gynæcoid woman has a characteristic physical shape, she has had a normal puberty and comfortable menstruation, and usually feels the well-known euphoria of pregnancy. She is seldom sick or complains of the common minor discomforts. Most of these women have a normal labour not only because of a normal structure but also because the uterus acts well throughout. Pain is minimal and the perineum dilates without serious tearing. Later the gynæcoid woman lactates well and quickly falls pregnant again. Though there are naturally exceptions, it is mostly true that if during the antenatal visits we can recognize a woman as clearly belonging to this type we can be satisfied that she will have good uterine function in labour. The opposite type is the android woman who lacks the characteristic figure and form of the first type. Her puberty may have been later than usual and often the menstruation has been painful, scanty and irregular. During pregnancy she is troubled with vomiting, vague pains in the abdomen, heartburn and many other minor discomforts. An occipito-posterior presentation is liable if she has an android pelvis, contractions are slow and feeble, there is much pain, with forceps delivery of varying difficulty and a chance of a deep perineal tear.

Uterine function can also be predicted by observation of the emotional attitude to labour, and this is as important as the recognition of the physical types. Many primigravidæ and also those who have endured the ordeal of a slow and difficult labour, with possibly a dead baby, begin their pregnancy in a state of ignorance, uncertainty and fear. Such women have had bad advice and often a mother-fixed childhood and adolescence. It is easy for a doctor with insight, sympathy and understanding to see through the shell of reserve and spurious courage. He can also predict that, should the state of fear persist unresolved, labour will be slow, painful, difficult and even hazardous.

The times of the antenatal visits give opportunities not only for the diagnosis of the physical type but also for an understanding of the woman's emotional state. We can do nothing to alter the physical type, but in both groups, especially the second in which fear is predominant, we can do much to prepare the mind and feeling by which fear can be exorcised and so uterine function liberated from the inhibition imposed by fear. After years of contact with pregnant women and labour I am firmly convinced that uterine function is closely related to the woman's mental outlook on childbearing. If a woman approaches and enters labour in a condition of uncertainty, lack of confidence, and therefore fear, the function of the uterus will be in disarray. Remembering that many of the minor handicaps of labour can be overcome by good uterine contractions, and also that the dangers of the more serious complications can be mitigated, I assert with conviction that the encouragement of function and less emphasis on structure will mark a new advance in the conduct of antenatal care. While I stress the importance, firstly of fear and failure in confidence, I would also suggest that all the other normal physiological processes should be remembered. So far there is no evidence that nutrition has any influence on actual uterine function though it is certainly a serious factor in the release of labour before its appointed term, with the delivery of feeble premature babies.

The diet of pregnant women in this country since 1939 has been a special care, and I think we owe to this something of the reduction in the number of stillbirths and neonatal deaths. It is indeed unusual to find a pregnant woman who is unmistakably undernourished in these days, though I do believe, perhaps wrongly, that they do not get enough protein. It is important, in my view, to encourage her to eat all the meat, fish, cheese, eggs and milk that she can find. Physical exercises during pregnancy have taken a place in antenatal care during the last few years in many hospital clinics. I am sure of the value of this form of prophylaxis, not only by reason of physical advantage but also because the woman feels that she is contributing something to preparation for labour and so gains a feeling of confidence in the value of her own positive efforts.

The tangible reality of such details as measurement, X-ray diagnosis, presentation and the other physical signs of the pregnant woman may satisfy our minds as we look for the grounds of prognosis, but the figures of the Registrar-General during the early 'thirties showed that this form of antenatal care was a failure. Whither, therefore, do we go from here? I repeat that we have not given enough attention to the part played in labour by uterine function. During pregnancy we can, by insight and experience, make a fair prediction of the probable course of labour, and by understanding, reassurance and confidence, do much to ensure that labour shall be easy and normal.

Professor W. C. W. Nixon: The half-century has almost turned since Ballantyne (1901) published his article—"A plea for a pre-maternity hospital"—containing the first suggestion of an antenatal clinic or hospital. During these fifty years opinion and practice have changed, in some instances swinging a full circle, so that it is time to reflect upon "whither" we are tending.

I can recall over a quarter of a century ago, when I was a student under Mr. Aleck Bourne, his plea for a shift of emphasis from structure to function, in relationship to the parturient woman. The mechanistic approach was in vogue at that time. It still exists in some places but there is in others an awakening to the importance of the holistic attitude towards the individual. The woman must be taken as a whole since her psyche and soma are so interwoven that neither can be neglected at that most critical time of her life, namely, pregnancy.

Mr. A. J. Wrigley stirred the complacency of the mid-thirties when he showed that antenatal care was failing. Meddlesome midwifery had shifted from the labour room to the antenatal department with results sometimes disastrous to both mother and baby, especially in the instance of induction of labour. Mr. Wrigley had as his senior colleague at St. Thomas's Hospital the late Dr. John Fairbairn, who was responsible for the introduction of the term "constructive hygiene" of pregnancy and who tried so hard to convert to this attitude those doctors and midwives who had charge of pregnant women.

These were the beginnings of the new attitude towards pregnancy. The cynicism of Mauriceau and his view of pregnancy being a disease of nine months' standing was no longer supportable. Unfortunately, in some quarters this emphasis on the abnormal rather than the normal still exists. The normal pregnancy and the normal delivery have not the drama of the abnormal, and the assistant, student or midwife gaining experience finds life dull when the week has passed without any untoward incident.

We are all aware of the importance of nutrition and it is in the antenatal clinic that so much can be taught in a practical way if a Food Advice Bureau is included in the service. In view of the prevalence of nutritional anæmia the hæmoglobin of every mother should be estimated at her first visit and again at the 36th week. The importance of adequate hæmoglobin has been confirmed by Wills and others (1947) who have shown the value of iron

therapy in maintaining a normal hæmoglobin level and thus reducing post-partum hæmorrhage.

For some years routine weighing of pregnant women has been the practice in some clinics. But is it really such a valuable aid in the early diagnosis of toxæmia? Ambrose Rogers, Lecturer in Mathematics at University College, and J. G. Dumoulin, Assistant in the Obstetric Unit, have analysed the weights of two groups of mothers during 1948 (Fig. 1).

Weight increases regarded as excessive by arbitrary standards A and B, in lb.:

Periods in weeks	1	2	3	4	5	6	7	8
Standard A	4	6	8	10	12	14	16	18
Standard B ..	3	5	6	8	9	11	12	14

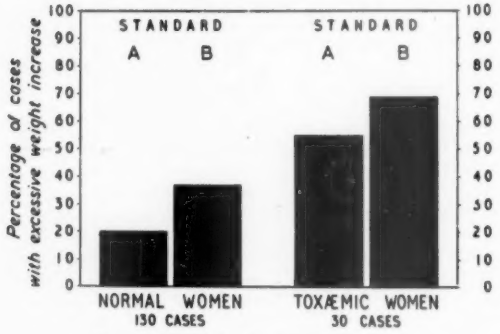


FIG. 1.—Weight in pregnancy.

This shows there is a tendency for toxæmic mothers to put on more weight than the mothers having normal pregnancies. But owing to the large standard deviation of the increase it is not much use as a diagnostic aid. It is often wrong to regard an excessive weight increase as indicative of toxæmia. We believe that the time spent on routine weighing could be better spent in giving advice about pregnancy.

During the past two years we have arranged that every mother should have a routine chest X-ray. Mr. T. Ealand, Assistant in the Obstetric Unit, has analysed the figures during this time (Table I).

TABLE I.—ROUTINE CHEST X-RAY EXAMINATION OF EXPECTANT MOTHERS, JANUARY 1946 TO AUGUST 1949, UNIVERSITY COLLEGE HOSPITAL

Total number of mothers examined		3,581
No. of cases of pulmonary tuberculosis discovered by X-ray examination ..		28 (0·74%)
Active	13	
Inactive	15	
Incidence of pulmonary tuberculosis in pregnancy, including those cases known to be infected before pregnancy..		2·61% (95 cases)

It will be seen that 28 cases (0·74%) of pulmonary tuberculosis were detected by this routine X-ray. All these cases had had the usual chest examination by the house surgeon and in only one were any abnormal signs discovered by this physical examination. I feel that routine chest X-ray of pregnant women should become obligatory.

Version.—To turn or not to turn? Mr. Dumoulin has shown from figures he has collected from 1947 and 1948 that there is a place for external cephalic version as a treatment for a breech presentation discovered in pregnancy. Version should be tried first without an anæsthetic; if it fails, then it should be tried again under anæsthesia.

These points are most important, as is the customary attention to the pelvis, the engaged head, the blood pressure, the urine and so forth.

But all this does not make up the whole picture. We cannot neglect the part that fear plays in the birth process. At University College Hospital we have found that one way of lessening this fear is by holding special classes for our mothers. Dr. Shila Ransom, anæsthetist to the Obstetric Unit, is responsible for their organization. In these classes, we find that simple explanations of the changes in pregnancy and of the birth process go a long way to increase confidence. As is well known, it was Dr. Dick Read who pointed out the importance of the pain-fear-tension syndrome. The physiotherapist at the special classes

teaches various types of breathing, posture and exercises. The exercises which we use are those elaborated by the late Mrs. Helen Heardman, who did so much to advance the idea and practice of natural childbirth.

Antenatal preparation along these lines, based directly upon the work of some of our compatriots, has been carried out with most successful results by Goodrich and Thoms (1948) of Yale University.

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Mr. A. J. Wrigley: There are some aspects of prenatal care in which I have seen changes occur in the last twenty-five years, or in which I would have wished to have seen changes occur.

My first observation is that at long last there are signs that the general health of the patient deserves, and is getting, an ever-increasing attention. Clinics still exist today where one person examines all the specimens of urine, another rushes round with a manometer and finally the "Chief" goes from couch to couch performing an abdominal examination. The patient as an individual need not exist. I tell students to answer the following question: "Which would you prefer to take charge of in her confinement—a healthy woman with a malpresentation or an unfit woman with a normal presentation?" The answer is surely the former, and the moral is that in our prenatal care we must place more emphasis on the general health of the patient.

In late years sincere and energetic measures have been adopted to try to prepare the woman both physically and mentally for her first labour. The physical side is dealt with by instruction in, and supervision of, the performance of remedial exercises designed to tone up the muscular structure of the whole body, to educate especially the muscles of expulsion, to teach correct stance, and to teach the patient how to relax. The first assessments of this work are beginning to come in and so far the results are hardly encouraging. Dr. Helen Rodway published a careful review of the results of physiotherapy in pregnancy on some 340 women who were confined at the Thorpe Coombe Hospital, Walthamstow. A comparison was made between these patients and a similar number of controls. There was no statistical difference between the two series. In 1948 similar analysis was made on 140 women at St. Thomas's. The results were almost identical in the exercise and control groups and the conclusions reached agreed with those of Dr. Rodway. In a further attempt to help our patients we have at St. Thomas's, since the analysis of the group of cases just mentioned, combined physiotherapy with what I may term a mild form of psychotherapy. Successive groups of patients who elect to join the classes in physiotherapy attend what may be called "talks by Sister". In these talks an attempt is made in the simplest language to explain the physiology and management of labour and the patients are taken to see the wards and nurseries. We have made a similar analysis of the results in some 106 women who have been delivered after going through the combined course. The results are identical with a similar number of controls. I have no doubt that prenatal education or treatment, call it what you like, on these lines is in its infancy and that the crest of its wave will not be reached for some years to come. Nevertheless, I venture to suggest, and to put on record, that the results will fall far short of expectations and give rise to great and widespread disappointment.

I now turn to three minor points. I first wish to refer to the performance of external cephalic version of a breech presentation in pregnancy. A great deal of consideration has been given to this successful piece of prophylactic medicine. We have appreciated that the cause of the malpresentation is at any rate worth a thought, that often no cause exists other than that the fœtus is premature, that in consequence version is often unnecessary before the 34th to 36th week of pregnancy, that its performance is fully justified by the advantages likely to accrue to the baby and mother, and lastly that in its performance, especially if the patient is anæsthetized, no great force should be used. If these conditions are observed, and if a sensible anæsthetic is used, I believe this item in prenatal care will in the future confer still greater benefits.

Next I hope that in the years to come much unnecessary anxiety, and discomfort from pointless and ineffective medical inductions of labour, will be avoided by a more common-sense outlook to what we term the "expected date of delivery". Let us realize that, at the moment at any rate, we are not all made alike, and that whereas most women will mature a fœtus of normal weight in a pregnancy lasting about 40 weeks, there are many exceptions both in the weight of a fœtus that is mature and in the length of time necessary to bring it to this state. Therefore we meet constantly women who will bring to a state of maturity a

big baby, or a normal baby, or a small baby, in a pregnancy of under 40 weeks' duration, or of 40 weeks' duration, or of over 40 weeks' duration.

Next I wish to suggest that in the future less, and not more, attention is given to the prenatal preparation of the patient for breast feeding. Other than a cursory observation that the breast anatomy appears reasonably normal, and a casual observation that I suppose there is no doubt that the woman accepts breast feeding as the natural thing to do, I advocate that nothing be done with patients under my care. I regard as unnecessary, and indeed undesirable, all treatment of the skin with either spirits or ointments and all massage of the breasts. The prenatal use of expression and nipple shields as advised by Dr. H. K. Waller would appear to be most successful in hospital practice where a routine in breast feeding is necessary.

X-ray examination of the bony pelvis and X-ray pelvimetry.—The possible disadvantages and dangers of this method are well known, but as the result of years of painstaking observations by workers such as Rohan Williams, Chassar Moir and others in this country our knowledge has increased enormously. The technique of radiography has improved, the risks of misinterpretation of the films have decreased, and the undoubted assistance of X-rays to a clinical examination has been demonstrated. An X-ray examination should be made of the pelvis of every woman embarking on her first pregnancy, and the results interpreted by a skilled worker.

I have left to the last the point I consider the most important. Indeed, I believe its importance to be such that unless a complete change of policy is accomplished, all our efforts to improve upon our clinical work are wasted and are set at nought. It is necessary for me briefly to refer to what I may term the evolution of our antenatal work up to July 5, 1948.

In the early 1920s a tremendous fillip was given to the efforts of the teaching schools by the appreciation of the value of prenatal care by the public health authorities. Their efforts resulted in the establishment of clinics all over the country. Numbers were all that mattered, and indeed it would appear that more credit was to be gained by the number of attendances made at such clinics than by any other criterion. Little or no attempt was made seriously to assess the value of the work—it was assumed that the value was immense—almost sacrosanct in fact: it appeared not to matter who took the clinic as long as the man or woman in charge was a registered medical practitioner. A most pernicious system was quickly established whereby the antenatal officer was completely detached from the subsequent events of the confinement. I know what I am talking about because I have suffered at both ends of this string. For some years I worked as Antenatal Officer to a large borough. Similarly, and for many more years, I have worked at what may be termed the recipient end. At times I would have been frankly amazed at what can only have been the attitude of complete indifference on the part of the medical officer in charge of a borough clinic had I not experienced myself the sense of detachment and frustration inherent in the conduct of antenatal clinics that were utterly divorced from the bedside and lying-in wards. I would here note that I am fully appreciative of the benefits conferred on the patients by the establishment of numerous antenatal clinics throughout the country. They save travelling, and their most important social workers establish a local knowledge and liaison. But this does not mean that the medical officers must be divorced from their colleagues working under the Regional Boards or Teaching Hospitals.

When, a few years ago, it became certain that a National Health Service was to be established, many of us were sure that this arrangement would be abolished. Alas, the state of affairs now is worse than it was five years ago. The gap between the Local Authority antenatal care and the Regional Board confinement is greater than ever. Before 1948 this arrangement could at least claim that its inception was entirely fortuitous, but under the National Health Service the splitting of the care of the pregnant woman has been deliberately planned. Such planning can never have been in the interests of National Health. I have dwelt on this subject at some length for I believe that as long as the present system obtains and the care of the woman in her pregnancy and confinement remains divided we are largely wasting our time in the consideration of other and clinical details.

Mr. Arnold Walker said that he objected to Mr. Wrigley's condemnation of Local Authority antenatal clinics. While no one has claimed that the separation of antenatal from intranatal care is satisfactory, it must be remembered that this service was developed because it was the only way in which the great majority of pregnant women could get reasonable supervision during their pregnancy and the best way in which the social and educational aspects of antenatal care could be provided. Those who have staffed these clinics in the past have done excellent work and there is a real place for them in the future. Mr. Wrigley also condemned "routine" visits to the clinics. Surely the detection of early toxæmia is almost

entirely a matter of routine, requiring office organization and a follow-up system. Antenatal services must be brought to the patient and her visits must be made easy and attractive. The examinations at the clinic are almost entirely a matter of routine but her visits provide an ideal opportunity for educating her in the tasks that lie ahead. What is needed is not the abolition of the local clinics but their proper correlation with the hospital, the general practitioner and the midwife.

With regard to antenatal exercises, he was sceptical about their value and considered that before much money and effort are expended on this refinement of antenatal care, its value should be proved by a scientific analysis of the results obtained by selected clinics.

Dr. C. V. Pink said that antenatal care should begin as soon as a baby girl is born for the attitude of the mother to childbirth certainly gets across to her children and we did not know how early in life the influence would act.

In Stonefield Maternity Home, the work had been developed on lines very similar to those described by Professor Nixon. The results have been very obvious in more quick labours, less shock and hæmorrhage, less need for inhaled anæsthetic and a forceps rate reduced to 3·4%. But much more important—the elimination of fear permits a woman to become intensely happy in the birth and to appreciate its deep significance as one of the major events of her life.

Dr. Pink was not surprised to hear that statistics show no reduction of hæmorrhage, &c., in units where "exercises" have been introduced; for success a fully integrated team of obstetrician, physiotherapist, and labour-ward nursing staff is necessary. He was just old enough to have seen the difference in midwifery when the antenatal clinics were organized in London about twenty-five years ago. He believed the development Professor Nixon had described constituted a step forward of equal magnitude and that the next generation would so appraise it.

Dr. John Burton: The present system of antenatal care involving Local Authority, general practitioner and hospital antenatal clinics inevitably led to some interruption of continuity of care, but this might equally well happen within any hospital. One of the main values of antenatal clinics was the education of women for motherhood when their interest is centred on this subject. In this field, the Local Authority clinics and certain hospitals are well equipped and progressive. It was unlikely that general practitioners would ever have the time to carry out such work.

This education of the mother should be attacked by all methods, physical and emotional, through exercise, talks and discussions and this work should be done by the antenatal team of midwife, health visitor and if necessary, physiotherapist.

In order to co-ordinate this service with general practitioner midwifery, health centres as envisaged by the Act are essential.

Miss Margaret Smith speaking as a physiotherapist said that there were two points of particular interest to her, namely, function as stressed by Mr. Bourne and relaxation, by Professor Nixon.

Physiotherapists had a special interest in *function* and felt that it was their particular job to help to improve function wherever possible. It was, therefore, one of the chief aims of the physiotherapist in antenatal training.

With reference to relaxation, she had found that patients much appreciated help in learning how to relax. They were encouraged to relax for a short time during the day as well as to relax the whole body on going to bed. Patients reported that they were able to sleep much better and that they suffered less from fatigue during the day.

Dr. Elizabeth Tylden asked for a closer collaboration between obstetrician and psychiatrist.

In reviewing 50 cases of mental upset during pregnancy and the puerperium certain things became apparent. First these disorders are an expression of the previous personality and experience of the individual woman. Second, they all have one thread running through them. They are an exaggeration of the general psychological change which always occurs during these times: a change which is generally recognized, but is difficult to define.

She asked for a more early recognition and treatment of the precursors of puerperal insanity. She would ask the meeting to take very seriously, and treat psychologically, the woman who is more sleepless than the average, the woman who is more afraid than the average of childbirth and the woman who shows a pathological aversion to, and loathing of the natural process of breast feeding. The causes for all these symptoms lie far in the past, as well as in the present situation.

The answer to many of the problems mentioned lay in a combination of the two agencies discussed by Mr. Arnold Walker and Professor Nixon. On the one hand, "individual psychotherapy" as one might say; the careful attention of one person who inquires intimately into the patient's whole past and present states. On the other hand, the classes and group instruction of U.C.H. represented "group psychotherapy", the acquisition of necessary information and sharing of it with others which can make the patient aware before delivery that others are going through the same experiences as herself.

The Americans have made several attempts to team together the obstetrician and the psychiatrist, and have discovered certain things. Mainly the immense influence of apparently minor ill-calculated remarks in precipitating a major crisis. She would like to see disappear the attitude in some midwives that a woman because she is in labour becomes mentally deficient. Praise and blame have no place in the proper conduct of labour. Too often the precipitating cause of breakdown has been a sense of shame at failing to breast-feed after repeated exhortations, or a feeling of shame at reacting to pain, induced by the scoldings of one who has not personally experienced that pain but exhorts the patient to pull herself together. Such exhortations must be replaced by an understanding of why particular sorts of behaviour occur.

Dr. A. J. Martin felt that too much accent was placed on the actual anatomical side of labour and on the incidence of abnormal conditions in regard to the evaluation of antenatal teaching. He found that in the women attending antenatal classes at the Royal Free Hospital there had been a marked reduction in the incidence of backache and that many stated that they felt "better in themselves", even when attending after the day's work. He felt that a great deal of the value of classes on Mrs. Heardman's lines was the removal of fear of the unknown.

Dr. Martin said that there was a difference between the antenatal training as advocated by Sister Randall and that of Mrs. Heardman, the former being largely concerned with position and labour, with the accent on exercises, while Mrs. Heardman's technique was largely concerned with relaxation, correct breathing and general education in the physiology of pregnancy, with the idea of removing the normal woman's nervousness.

Dr. Edward Cope said that much emphasis had been placed upon the importance of antenatal exercises, particularly those suggested by Grantly Dick Read and taught at University College Hospital and elsewhere by the late Mrs. Heardman, which purport to promote muscular relaxation, and allow an easy and smooth delivery.

Some years ago Mrs. Heardman organized antenatal classes at the Leeds Maternity Hospital and, in addition, a twenty-four-hour service was instituted for the continuance of treatment during labour. During two years' residence at this hospital, he was able to form some impression of this work. There appeared to be no reduction in mortality and morbidity of patients treated in this way.

Professor A. M. Claye in a lecture delivered at the R.C.O.G. states that he has seen no figures which confirm the view expressed by Dr. Grantly Dick Read, that the incidence of lacerations of the soft parts and of post-partum hæmorrhages are reduced. He analysed the records of 100 recent primigravidæ who had attended the classes and of 100 controls and there was no significant difference in the figures for perineal tears, cervical tears and episiotomies. His opinion is that the benefit is mental rather than muscular.

Many speakers had preferred to keep the discussion on a high plane and avoid mere statistics. However, one had always understood that the success or failure of antenatal care could best be assessed in terms of maternal and fœtal mortality and morbidity. Mr. Aleck Bourne deplored the high incidence of surgical inductions in past years and quoted 6% as a peak figure. In this connexion he would like to quote induction figures from the Churchill Hospital, Oxford. This was a new unit under the directorship of Mr. John Stallworthy.

In 1948 there were 752 deliveries, an induction rate of 7%, a stillbirth-rate of 16 per 1,000 deliveries and a neonatal death-rate of 10·6 per 1,000 deliveries.

In 1949 (up till October 18) there were 762 deliveries with an induction rate of 16%, a stillbirth-rate of 5 per 1,000 deliveries, and a neonatal death-rate of 14·6. The Cæsarean section rate of the whole series was 0·8% and the forceps rate 6·92%. There had been no maternal deaths.

There were no inductions for disproportion, the majority being for pre-eclampsia and postmaturity. It will be seen that despite the increase in surgical inductions there has been a 25% reduction of fœtal wastage, and of the four stillbirths in 1949 at least two could have been saved by earlier induction.

Section of Epidemiology and State Medicine

President—W. H. BRADLEY, D.M., M.R.C.P.

[*October* 21, 1949]

DISCUSSION: THE INTEGRATION OF PREVENTIVE HEALTH SERVICES. [*Abridged*]

Dr. A. T. Elder, *Deputy Chief Medical Officer, Ministry of Health and Local Government, Northern Ireland.*

Of recent years few words have been bandied about in official language with such frequency and so little effect as the word "Integration". The Concise Oxford Dictionary defines the verb as meaning "to complete (imperfect thing) by the addition of parts or to combine (parts) into a whole". Chamber's Twentieth Century Dictionary introduces the meaning "to renew", and this is supported by several other dictionaries. Whether we accept these meanings or appeal to the Latin origin, we are forced to the logical conclusion that if a need for integration of something exists then that something is at present incomplete or "requiring to be renewed".

We in Northern Ireland have adopted a way of life in our Preventive Health Services differing in some measure from that followed in Great Britain. I shall describe in simple terms only those ideas which we have adopted in the past few years as making for this sense of completion or renewal of vigour of which I have spoken, and to explain what merit we think lies in them. When we consider the relative size of populations involved, it becomes clear that what may produce a fair measure of success in a smaller population may not be equally applicable to the larger. Nevertheless the lessons to be studied are in large measure the same. I will deal with but some of the major ideas we have adopted, though this does not by any means cover the field of endeavour.

The transfer of School Medical Services.—When the Public Health and Local Government (Administrative Provisions) Act (Northern Ireland), 1946, established the functions of the new Health Authorities with their Statutory Health Committees, provision was incorporated in the Act for the transfer by means of Statutory Instrument of the central control of the health of school children from the Ministry of Education to the Ministry of Health and Local Government at an appropriate time and with the consent of the former Ministry.

Four sections only were transferred, and in such sections for *Education Ministry* we now read *Health Ministry*, and for executive purposes for *Education Authorities* we read *Health Authorities*. The sections involved were those dealing with: (*a*) the ascertainment of physically handicapped children, from whatever cause the disability might arise, and this ascertainment to be lawful amongst children from age 2 years upwards; (*b*) the provision of medical inspection and treatment—this to include the voluntary and grammar type of school; (*c*) the power to ensure cleanliness amongst school children, including the control of vermin infestation; and lastly (*d*) the ascertainment of children considered to be ineducable due to disability of mind.

Subsequent to the Appointed Day the Ministry of Health produced its School Medical Regulations based on these four sections of the Education Act. The School Medical and Dental Records approved in England were adapted for use in Northern Ireland and issued through His Majesty's Stationery Office to the Health Committees. Provision was made for research within the framework of the School Health Service, as is the case in the Scottish Regulations, and in addition the School Health Record

Cards are made available on request, and by Statute, on the individual ceasing to be a pupil at school-leaving age, to recognized medical attendants who may be: (*a*) the family practitioner; (*b*) a medical officer employed by the Northern Ireland Hospitals Authority or the Tuberculosis Authority; (*c*) an Examining Surgeon (factory M.O. under the new Act) under the Northern Ireland Factories Act, 1938; or (*d*) a Medical Officer to any University or other educational establishment.

Dental records are made available to dental practitioners under contract to the Northern Ireland General Health Services Board.

Health propaganda having been laid as a duty upon Health Authorities by the Health Services Act of 1948, health education in schools again now falls to the Health Authorities.

As to the officers necessary to the adequate prosecution of this service a loophole had been made in the previously mentioned "Administrative Provisions" Act for the appointment by each Health Committee of such additional officers as might become necessary for the efficient carrying out of the functions of the Committee. Under this section the Divisional County Medical Officer of Health becomes also the Area School Medical Officer, the Health Visitor becomes the School Nurse, the Sanitary Officer ascertains the hygiene and sanitary condition of schools, and so on, and a similar practice obtains in the County Boroughs.

It may be asked why only four sections of the Education Act were transferred.

It was considered wise to leave the administration of the School Meals and Milk Service with the Education Authorities, because of its close association with the everyday school life of the child, and the special interest of the teaching profession.

The health aspect of this catering service, organized as it is through the medium of catering advisers, is amply dealt with by way of an advisory service for the Medical Officer of Health in regard to the nutritional aspects of school meals and the preventive measures necessary to the hygienic control of school canteen food preparation.

The safety of school milk was provided for by means of Regulations passed by the Ministry of Education under which all milk supplies to schools are subject to the approval of the appropriate Medical Officer of Health, and may be stopped because of an outbreak of disease or uncleanliness on his authority alone. He takes action and subsequently notifies the appropriate Ministry, in this case the Ministry of Agriculture in Northern Ireland.

Executive action in regard to the remedying of hygienic defects in schools is vested in the School Managers, in many instances this means the Ministry of Education, and is enforceable by the local sanitary authority under the Public Health Acts. It will be noted that the initiative in this action comes, in the first place, from the Ascertainment Officers of the Health Committees, that is, the School Medical Officer and his Sanitary Officer.

The provision of nursery classes and schools remains with the Education Committees and the ordinary School Personal Health Service applies here.

Having ascertained the numbers of pupils who are suffering from physical handicaps the Health Committee makes representations to its appropriate Education Committee in regard to the schooling appropriate to each type of child ascertained, and the provision of such special schools as may be necessary remains with the Education Committees. Where such provision for reasons of economy clearly involves the areas of several Committees, and indeed for some disabilities, the entire Province, consultation takes place at Ministerial level between "Health" and "Education" in the first instance. At health authority level close liaison exists between Medical Officers of Health and Directors of Education, and the Medical Officer of Health may attend education authority meetings as occasion may demand.

The scheme thus outlined has been expanding and developing over the past two years and so far has proved to be a very happy and efficient service. Of the elementary

school population 98% are in receipt of free milk supplies (95% of this is pasteurized milk). If the School Meals Service is not as far advanced as this it is not due to lack of energy on the part of Directors of Education, but rather on account of lack of building materials and kitchen equipment.

The Northern Ireland Tuberculosis Authority.—Prior to 1948 the care of tuberculous persons had been vested in the local authorities as is the case in Great Britain. The Tuberculosis Act (Northern Ireland), 1947, created a new autonomous authority called the Northern Ireland Tuberculosis Authority in which now rests the control of tuberculosis in all its aspects, the prevention, as well as clinical treatment, of tuberculosis. The Authority has representatives from the Health Authorities, and for administrative purposes the day-to-day organization is centred on a director who is a medical man, a deputy director, and a lay secretary.

The Province is divided into five dispensary areas, and each of these, together with the sanatoria of the area, is under the control of a tuberculosis officer and appropriate medical staff. Notifications of disease are sent to the area tuberculosis officer by the general practitioners, who, by regulation, notify not only proven but suspected tuberculosis. The operation of mass miniature radiography is vested in the Authority as is the B.C.G. vaccine service, and all matters relating to tuberculosis research. The Authority possesses its own research laboratory.

Necessary links have been established with the Medical Officers of Health and the Hospitals Authority. The appointment of specialists, such as thoracic surgeons, rests with the Northern Ireland Hospitals Authority in consultation with the Tuberculosis Authority.

The Tuberculosis Authority employs its own After-Care Officers who are duly qualified Health Visitors, but the home nursing of tuberculosis cases is catered for, in order to avoid duplication, by the Home Nursing Service of the Health Authority. This is a much simpler process than it sounds because all that is required is a written request for the services of a nurse to the appropriate Medical Officer of Health.

Compulsory vaccination.—The law in Northern Ireland is regulated principally by the Vaccination (Ireland) Act, 1863, and the Vaccination (Ireland) (Amendment) Act, 1879, and vaccination against smallpox remains compulsory to this day.

The percentage of vaccination related to total births registered was not 100% as might be inferred but was as follows:

1943, 69%; 1944, 70%; 1945, 80%; 1946, 76%.

The factor of importance in the operation of compulsory vaccination was that the "Conscience Clause" was never introduced in the Northern Ireland legislation. Occasional prosecutions for non-compliance with the law were usually followed by a spate of vaccinations.

During the past twenty years, during which period about half a million primary vaccinations would be carried out, only one confirmed case of encephalitis following vaccination, has come to official notice, and in this case the patient had been vaccinated with lymph which did not come from the usual source of supply.

Central Government medical and ancillary staffing.—The medical, dental, nursing, and sanitary staff of the Government is wholly employed by the Ministry of Health and Local Government. No other Ministry, such as Education, Labour, Commerce, Home Affairs, Finance, or Agriculture, possesses any medical and allied staff, and the Ministry of Labour is also the Ministry of National Insurance. As regards selection of staff to operate under the Chief Medical Officer, while each one may deal with a certain amount of general medical work, each has also some branch of the Government service in which he or she specializes. Thus, advice is afforded to other Ministries by the Health Ministry through administrative channels on matters of policy or where no urgency exists, and for routine inspections or urgent medical advice direct access to the professional officer concerned is readily possible.

Items are dealt with, therefore, under subject matter rather than by choice of individual, and no officer is seconded to another Ministry. For example, matters relating to epidemiology and hygiene will be advised upon by the Senior Medical Officer of that section, whether raised by the Ministry of Health, Agriculture (e.g. milk production) or Commerce (e.g. cafés, restaurants, &c., under Tourist Traffic Board). Again, child health whether in regard to Ministry of Health matters (Infant Welfare Clinics), Education (School Health), or Home Affairs (Deprived Children and Approved Schools) will be the concern of the Senior Medical Officer for Child Health.

A Senior Medical Officer for Mental Health advises on the mental health of school children, children in the care of homes and societies or approved schools, and also on those referable to the Hospitals Authority as ineducable in the ordinary way. He also performs the functions applicable to the former Board of Control and as Inspector of Mental Hospitals.

The Medical Referee Service comes directly under Ministry of Health and Local Government control.

The Chief Medical Officer is also Chief Medical Officer to the Ministry of Labour and National Insurance, Chief Medical Inspector of Prisons, and Chief Medical Adviser to the Ministry of Finance on Civil Service health.

An advisory link has been established with the Chair of Social and Preventive Medicine at Queen's University, Belfast, for matters of abstruse professional interest or research.

Industrial health.—A Medical Officer specially versed in industrial hazards is employed, with some part-time assistance, to act as a Referee under the Industrial Injuries Act, and to supervise the work of the Medical Boards. A warrant as Inspector of Factories was issued to him two years ago, but in addition warrants are also held by the Senior Medical Officer for Hygiene and Epidemiology, and the Chief Medical Officer and his Deputy. Thus the forms for inspection and matters of general policy have been advised upon, medically speaking, administratively, clinically, and from the public health point of view.

With regard to legislation, the Factories Act (Northern Ireland), 1949, provides for the substitution of a general practitioner by an officer of a Health Authority to the post of Examining Surgeon, with the approval of the Ministry of Labour when such a post becomes temporarily vacant, and also for the appointment of works doctors as Factory Medical Officers.

The sanitary aspects of all factories are controlled by the Health Authorities, and as far as factories not using power-driven plant are concerned all matters in relation to public health conditions of work are controlled by them.

Study of the relative number of actual hazards compared with the general hygienic conditions requiring survey in Northern Ireland shows that it might be rational to employ a hygiene-trained Medical Officer for the routine inspection of factories, with reference, where desirable, on matters of special hazard to the Medical Specialist Officer in Industrial Diseases.

After a brief reference to the General Health Services Board and Mental Health Service, Dr. Elder concluded by saying that it was for his hearers to judge whether the picture thus presented constituted a fair measure of integration in the real sense of the term. A tremendous amount of goodwill on the part of all Ministries was necessary, and financial considerations naturally played a large part in the determination of the pattern.

Dr. Dennis Geffen: Now that we have had over a year's experience of the National Health Service Act we should ask ourselves whether we have secured adequate integration of the Health Services.

The midwifery service.—The local health authorities are responsible for domiciliary midwifery. They may either employ the midwives themselves or they may contract with voluntary organizations or hospital management committees to provide the service for them. The hospital management committees must make provision for hospital confinements.

For domiciliary midwifery to be satisfactory there is need of a midwife and possibly a doctor, a flying squad associated with the obstetric department of a hospital, and hospital beds, both ante-natal and midwifery. I cannot see that there is any sense in leaving domiciliary midwifery with the local health authority with power to hand it back to the hospital management committee. It looks to me as if midwifery, both hospital and domiciliary, ought to be in the hands of the hospital management committees, who should also supervise the work of the domiciliary midwife.

Again, there seems to be some confusion between the domiciliary midwife, the general practitioner obstetrician and the doctor who may be called out at the wish of the midwife acting as such, and who will then be paid by the local health authority. At the present moment the general practitioner gets £5 5s. for making an ante-natal and post-natal visit and attending the confinement if required. For a general practitioner obstetrician the fee is 7 guineas. On the other hand, if a midwife acting as such should call in a doctor, he may be paid £4 14s. 6d. for an operative emergency, as for example the removal of a retained placenta, £2 12s. 6d. for a single visit during labour, or 3 guineas for suturing the perineum or resuscitating a baby, or for one visit during the daytime, 10s. 6d. All this seems nonsensical to me. It cannot be right to tell a doctor that, having received 7 guineas, there is no need for him to attend the confinement unless so requested. I should have thought that a better integrated service would have been the provision of a midwife under the scheme, with power to call out a doctor if necessary. It would be better still if the domiciliary midwifery service were provided by the hospital management committee, who would then back up its own midwives working on the district with the provision of medical assistance, a flying squad, second opinion, assistants and so on, through the wholetime hospital obstetric staff. If it be argued that normal confinements should be conducted by a midwife, then this should be the provision made by the National Health Service Act, and if a doctor is considered unnecessary or a luxury, his services as a domiciliary obstetrician should be outside the scope of the Act.

Maternity and child welfare.—There is no clean-cut line of demarcation between the duties of a local health authority and those of the general practitioner. Before the passing of the Act there was an obvious need for the ante-natal clinic, the children's clinic, the school minor ailment clinic and all its ancillary services, because they provided a service which otherwise was not available free of charge except to insured persons. To-day it must be remembered that if a mother needs advice regarding her children or minor ailment treatment she is entitled to it from her general practitioner under the National Health Service scheme. We therefore get the anomalous position of the school doctor or the child welfare officer being told to see a patient at a maternity and child welfare or school clinic but not to prescribe at the expense of the local health authority, but to refer the patient to her own doctor to get a prescription under the National Health Service Act. The alternatives are: to give advice only, which is administratively difficult, to scrap the clinics and send patients to the general practitioner, which is unwise, or to allow the doctors in welfare clinics and school clinics to prescribe under the National Health Service Act. This is the obvious solution. The difficulty lies in the fact that there would be two doctors prescribing for one patient, that is, the local health authority's doctor at the clinic and possibly a general practitioner. I think this is a theoretical objection for it could easily have occurred before July 5, 1948, yet in fact no difficulty did arise therefrom.

Health centres. These must be provided, maintained and staffed as far as non-professional personnel is concerned, by the local health authority. General practitioners will be supplied to work thereat by the local executive council; specialists by the hospital service. At these health centres many of the local authority's functions will be stationed. I cannot persuade myself that this manifold provision of services in one health centre is satisfactory, and the Government should make up its mind whether or not it really does want the local health authority to provide actual treatment services or whether it wants such services provided by them temporarily until such time as they can be taken over either by the local executive councils or the hospital service.

Infectious diseases.—Notification is to the medical officer of health of the local authority, be it a county borough, a non-county borough, an urban or a rural district council. Vaccination and immunization are the function of the county or the county borough. I think this is most unfortunate. Surely the medical officer of health who has to deal with the prevention of epidemic disease should also be responsible for and have all information concerning the immunity of the population whose health he protects.

Many of these difficulties have been got over administratively by appointing the district medical officer of health as assistant county medical officer. In some cases local committees, called area committees, intervene between the county medical officer and the assistant working in those areas. I do not think this promotes an integrated service throughout the whole county, and it certainly causes administrative delay and unnecessary expenditure.

Pædiatrics and obstetrics.—It is now proposed to divide maternal care from the care of children. Pædiatricians will look after children under 5 and school children, and obstetricians will conduct ante-natal and post-natal clinics. It is further suggested that pædiatricians shall be associated with a hospital for children or the pædiatric department of a general hospital, and obstetricians with a lying-in hospital or the obstetric department of a general hospital. This sounds easy but it does mean one person serving two masters.

The matter becomes still further complicated when we are told that in future our clinics should be manned by general practitioners in order that they may participate in the preventive health services. This means that we shall have a general practitioner receiving his fees from the local executive council, being paid for his clinic work by the local health authority, and yet also being on the staff of a special hospital and being paid thereby. He will have in fact three masters. If it is really the intention that pædiatricians shall look after children, and obstetricians the expectant and nursing mothers, then I think the clinics must be staffed and manned by the hospitals.

Incidentally, wholetime maternity and child welfare officers have been a success and I see no reason why they should be abolished.

The hospital service.—No local health authority now possesses hospital beds, and I think some of them are finding it extremely difficult to administer a service without the backing of beds. I know that there is liaison between Regional Hospital Boards and Local Health Authorities, but liaison with somebody who controls hospital beds is a very different story from controlling them oneself.

Now the Regional Hospital Boards have set up Management Committees to look after one, two or more hospitals. There would have been a better integration if the public health committees of the local authorities or of selected local authorities had been made the hospital management committees. In this way there would have been a wise integration of hospital and local authority services, still leaving the general control and planning of the hospitals to the Regional Boards, while avoiding the setting up of a large number of new committees and the employment of a large number of additional officers.

Section of Endocrinology

President—A. S. PARKES, M.A., Sc.D., F.R.S.

[*October* 26, 1949.

The History of the Discovery of Addison's Disease

By P. M. F. BISHOP, D.M.

THE PAPER TO THE SOUTH LONDON MEDICAL SOCIETY

A HUNDRED years ago, on Thursday, March 15, 1849, Dr. Addison, at the request of the President, John Hilton, proceeded to describe, before the South London Medical Society: "A remarkable form of anæmia, which, although incidentally noticed by various writers, had not attracted, as he thought, by any means the attention it really deserved. It was a state of general anæmia incident to adult males, and had for several years past been with him a subject of earnest inquiry and of deep interest. It usually occurs between the ages of 20 and 60; sometimes proceeding to an extreme degree in a few weeks, but more frequently commencing insidiously, and proceeding very slowly, so as to occupy a period of several weeks, or even months, before any very serious alarm is taken either by the patient or by the patient's friends. Its approach is first indicated by a certain amount of languor and restlessness, to which presently succeed a manifest paleness of the countenance, loss of muscular strength, general relaxation or feebleness of the whole frame, and indisposition to, or incapacity for, bodily or mental exertion. These symptoms go on increasing with greater or less rapidity: the face, lips, conjunctivæ, and external surface of the body, become more and more bloodless; the tongue appears pale and flabby; the heart's action gets exceedingly enfeebled, with a weak, soft, unusually large, but always strikingly compressible pulse; the appetite may or may not be lost; the patient experiences a distressing and increasing sense of helplessness and faintness; the heart is excited, or rendered tumultuous in its action, the breathing painfully hurried by the slightest exertion, whilst the whole surface bears some resemblance to a bad wax figure: the patient is no longer able to rise from his bed; slight œdema perhaps shows itself about the ankles; the feeling of faintness and weakness becomes extreme, and he dies either from sheer exhaustion, or death is preceded by signs of passive effusion or cerebral compression. In three cases only was there an inspection of the body after death, and *in all of them was found a diseased condition of the suprarenal capsules*. Dr. Addison inquired if it were possible for all this to be merely coincidental? It might be so, but he thought not, and making every allowance for the bias and prejudice inseparable from the hope or vanity of an original discovery, he confessed that he felt it very difficult to be persuaded that it was so. On the contrary, he could not help entertaining a very strong impression that these hitherto mysterious bodies—the supra-renal capsules—may be either directly or indirectly concerned in sanguification; and that a diseased condition of them, functional or structural, may interfere with the proper elaboration of the body generally, or of the red particles more especially. At all events, he considered that the time had arrived when he felt himself warranted in directing the attention of the profession to these curious facts."

THE 1855 MONOGRAPH

Little attention appears to have been paid to these observations, and it was six years before Addison himself again brought this condition to the notice of the medical profession by the publication of a short monograph "On the Constitutional and Local Effects of Disease of the Supra-renal Capsules" in the introduction to which he says: "There are still, however, certain organs of the body the actual functions and influence of which have hitherto entirely eluded the researches, and bid defiance to the united efforts of both physiologist and pathologist.

"Of these, not the least remarkable are the 'supra-renal capsules', the *atrabiliary* capsules of Caspar Bartholinus; and it is as a first and feeble step towards inquiry into the functions

and influence of these organs suggested by pathology, that I now put forth the following pages."

Every author who writes upon Addison's disease acknowledges that Addison's original description of the condition has not been improved upon either in respect of the accuracy and the thoroughness of his observations, or in the eloquence of his narrative. We shall do well therefore to browse for a few moments among the pages of what is undoubtedly one of the outstanding medical classics of the nineteenth century.

"It will hardly be disputed", it begins, "that at the present moment the functions of the supra-renal capsules, and the influence they exercise in the general economy, are almost or altogether unknown. The large supply of blood, which they receive from three separate sources; their numerous nerves, derived immediately from the semilunar ganglia and solar plexus; their early development in the fœtus; their unimpaired integrity to the latest period of life; and their peculiar gland-like structure—all point to the performance of some important office: nevertheless, beyond an ill-defined impression, founded on a consideration of their ultimate organization, that, in common with the spleen, thymus, and thyroid body, they in some way or other minister to the elaboration of the blood, I am not aware that any modern authority has ventured to assign to them any special function or influence whatever.

"To the physiologist and to the scientific anatomist, therefore, they continue to be objects of deep interest; and doubtless both the physiologist and anatomist will be inclined to welcome and regard with indulgence the smallest contribution calculated to open out any new source of inquiry respecting them. But if the obscurity which at present so entirely conceals from us the uses of these organs justify the feeblest attempt to add to our scanty stock of knowledge, it is not less true, on the other hand, that any one presuming to make such an attempt ought to take care that he do not, by hasty pretensions, or by partial and prejudiced observation, or by an over-statement of facts, incur the just rebuke of those possessing a sounder and more dispassionate judgment than himself.

"Under the influence of these considerations I have for a considerable period withheld, and now venture to publish, the few facts bearing upon the subject that have fallen within my own knowledge, believing, as I do now, that these concurring facts, in relation to each other, are not merely casual coincidences, but are such as admit of a fair and logical inference —an inference that, where these concurring facts are observed, we may pronounce with considerable confidence the existence of diseased supra-renal capsules.

"As a preface to my subject, it may not be altogether without interest or unprofitable to give a brief narrative of the circumstances and observations by which I have been led to my present convictions.

"For a long period I had from time to time met with a very remarkable form of general anæmia, occurring without any discoverable cause whatever—cases in which there had been no previous loss of blood, no exhausting diarrhœa, no chlorosis, no purpura, no renal, splenic, miasmatic, glandular, strumous, or malignant disease.

"Accordingly, in speaking of this form in clinical lecture, I perhaps with little propriety applied to it the term 'idiopathic' to distinguish it from cases in which there existed more or less evidence of some of the usual causes or concomitants of the anæmic state.

"It makes its approach in so slow and insidious a manner that the patient can hardly fix a date to his earliest feeling of that languor which is shortly to become so extreme. The countenance gets pale, the whites of the eyes become pearly, the general frame flabby rather than wasted; the pulse, perhaps large, but remarkably soft and compressible, and occasionally with a slight jerk, especially under the slightest excitement; there is an increasing indisposition to exertion, with an uncomfortable feeling of faintness or breathlessness on attempting it; the heart is readily made to palpitate; the whole surface of the body presents a blanched, smooth and waxy appearance; the lips, gums, and tongue seem bloodless; the flabbiness of the solids increases; the appetite fails; extreme languor and faintness supervene, breathlessness and palpitations being produced by the most trifling exertion or emotion; some slight œdema is probably perceived above the ankles; the debility becomes extreme. The patient can no longer rise from his bed, the mind occasionally wanders, he falls into a prostrate and half-torpid state, and at length expires. Nevertheless, to the very last, and after a sickness of, perhaps, several months' duration, the bulkiness of the general frame and the obesity often present a most striking contrast to the failure with exhaustion observable in every other respect.

"With perhaps a single exception the disease, in my own experience, resisted all remedial efforts, and sooner or later terminated fatally.

"It was whilst seeking in vain to throw some additional light upon this form of anæmia that I stumbled upon the curious facts which it is my more immediate object to make known to the profession; and however unimportant or unsatisfactory they may at first sight appear, I cannot but indulge the hope that, by attracting the attention and enlisting the co-operation

of the profession at large, they may lead to the subject being properly examined and sifted, and the inquiry so extended as to suggest, at least, some interesting physiological speculation, if not still more important practical indications.

"The leading and characteristic features of the morbid state to which I would direct attention are, anæmia, general languor and debility, remarkable feebleness of the heart's action, irritability of the stomach, and a peculiar change of colour in the skin, occurring in connexion with a diseased condition of the 'supra-renal capsules'. We discover a most remarkable and, so far as I know, characteristic discoloration taking place in the skin —sufficiently marked, indeed, as generally to have attracted the attention of the patient himself or of the patient's friends.

" This discoloration pervades the whole surface of the body, but is commonly most strongly manifested on the face, neck, superior extremities, penis, and scrotum, and in the flexures of the axillæ and around the navel.

" It may be said to present a dingy or smoky appearance, or various tints or shades of deep amber or chestnut-brown; and in one instance the skin was so universally and so deeply darkened that but for the features the patient might have been mistaken for a mulatto.

"In some cases the discoloration occurs in patches, or perhaps rather certain parts are so much darker than others as to impart to the surface a mottled or somewhat chequered appearance; and in one instance there were, in the midst of this dark mottling, certain insular portions of the integument presenting a blanched or morbidly white appearance, either in consequence of these portions having remained altogether unaffected by the disease, and thereby contrasting strongly with the surrounding skin, or, as I believe, from an actual defect of colouring matter in these parts.

"This singular discoloration usually increases with the advance of the disease; the anæmia, langour, failure of appetite, and feebleness of the heart, become aggravated; a darkish streak usually appears on the commissure of the lips: the body wastes, but without the emaciation and dry, harsh condition of the surface, so commonly observed in ordinary malignant cases; the pulse becomes smaller and weaker; and without any special complaint of pain or uneasiness the patient at length gradually sinks and expires."

The State of Knowledge Concerning the Adrenal Glands Before 1849

Addison himself indicated, in the passages which I have just quoted from his monograph, that "the functions of the supra-renal capsules, are almost or altogether unknown". In the beautiful copperplates of human anatomy which Eustachius completed in 1552, but which were preserved in the Vatican Library until Pope Clement XI gave them to his physician Lancisi for publication in 1714, the adrenals are shown. Jean Riolan, bitter critic of William Harvey, named them the "supra-renal capsules" in 1629, though some years previously in Copenhagen, Caspar Bartholinus the elder, grandfather of that Caspar Bartholinus who described the vaginal glands, believed they contained black bile in their "cavity". A hundred years later the Académie des Sciences of Bordeaux offered a prize for an essay on "Quel est l'usage des glandes surrénales?" Apparently no one could put forward even a plausible theory, for the adjudicator recommended that the prize should not be awarded.

Another hundred years later in 1841, François Magendie, the physiological mentor of the great Claude Bernard, made the somewhat enigmatic remark that as no one believed any longer in black bile, the adrenals "had ceased to be secreting agents".

The comparatively large size of the organs in the fœtus had led to the suggestion that they were the fœtal kidneys, which ceased to have any function after birth.

Development of Knowledge of the Adrenals Subsequent to 1849

Addison's brilliant discovery was like a comet in a starless sky. It flashed across the scene and disappeared. Some people, especially in this country, even denied its existence. The prophet was not to be without honour, however, for Trousseau in 1856, the year after the publication of the monograph, named the condition "La maladie d'Addison" and that impetuous and ebullient figure Charles Edouard Brown-Séquard lost no time in collecting together fifty-one rabbits, eleven dogs, cats, mice and pigs, and depriving them of their adrenals, insisting when they all succumbed that they had died of Addison's disease and that the adrenal glands contained a life-preserving material. This, the first conception of an endocrine secretion, was looked upon with scepticism by some of Brown-Séquard's contemporaries, who were used to the sudden changes in his chequered career, and the wild ideas that chased each other through his impulsive mind, and they were inclined to attribute the death of his animals to more cynical causes.

From 1856, when Brown-Séquard performed his classical experiments, onwards for

nearly forty years nothing further was added to the knowledge of the adrenals. In 1894 Oliver and Schäfer demonstrated the presence of a pressor substance in the adrenal medulla. In 1901, Takamine and Aldrich independently isolated adrenaline in crystalline form, Aldrich giving it the empirical formula of $C_9H_{13}NO_3$; and in 1904 Stolz synthesized it. It thus became the first hormone to be chemically isolated, have its structure established and to be synthesized. In 1917 Rogoff and Stewart began the series of researches which established cortical extracts as possessing life-preserving properties. In 1919 Cannon propounded his "emergency" theory of adrenal medullary function. In 1928 Szent-Györgyi embarked upon his search for a powerful reducing agent in the adrenal cortex and ended up by discovering vitamin C. In 1930 Swingle and Pfiffner prepared a cortical extract which maintained life in adrenalectomized dogs and which was subsequently employed in the treatment of Addison's disease. In 1936 Kendall isolated corticosterone in crystalline form. In 1937 Reichstein prepared deoxycorticosterone acetate synthetically. In 1938 Simpson employed it in the treatment of Addison's disease. In 1946 17-hydroxy-11-dehydro-corticosterone (Kendall's Compound E) was prepared from deoxycholic acid by Sarrett, working at the Merck Research Laboratories, and in 1949, exactly one hundred years after Addison was addressing the South London Medical Society, Philip Hench, of the Mayo Clinic, made the startling announcement that Compound E or "cortisone" could completely relieve the symptoms of rheumatoid arthritis.

The Background of Addison's Discovery

Was Addison's discovery a lucky chance, or did he deserve the fame it has subsequently bestowed upon his name?

Undoubtedly the condition was not a new disease. Marañón, the great Spanish physician, endocrinologist and historian, has diagnosed in retrospect a case of Addison's disease in a priest at Escorial, the hamlet where Philip the Second was later to build in the shape of the grill on which St. Lawrence was martyred, that magnificent edifice, part monastery, part cathedral, part palace, in gratitude for the victory of St. Quentin. The monk's illness occurred in 1554, the year that Mary of England became Philip's wife.

Addison was lucky not to have been forestalled on at least five occasions. In his own hospital his senior colleague, the great Richard Bright, had, as early as 1831, observed and recorded a case of Addison's disease, and had preserved the adrenal glands which were tuberculous. Addison, in reporting on this case again, in his 1855 monograph, writes : "It does not appear that Dr. Bright either entertained a suspicion of the disease of the capsules before death, or was led at any period to associate the colour of the skin with the diseased condition of these organs, although his well-known sagacity induced him to suggest the probable existence of some internal malignant disease." In 1823, Schotte recorded a typical case, and Kirkes also described a case before Addison's monograph was published. In 1856 Sibley recorded another case at the Middlesex Hospital. In 1846, Aran published a series of cases of supposed pancreatic disease one of which is given in full detail and is clearly a case of Addison's disease. Aran, however, mistook the site of the abscess found on opening the abdomen at autopsy. The pus originated in the adrenal, but he thought it came from the pancreas.

Addison's achievement was in realizing that the adrenal disease was the cause of the clinical syndrome which he so vividly described, and the following considerations will show that this was no lucky coincidence.

(1) *Addison as a Dermatologist*

In the first place, Addison was especially intrigued by the pigmentation in this condition because he had a singular interest in skin disorders and might well have made a name and a fortune for himself as a dermatologist had he so wished. It is, however, one of the paradoxes of this fascinating story that the founder of clinical endocrinology abhored specialism in medicine. He had studied under Thomas Bateman, the disciple of Robert Willan, the founder of British dermatology, and the mantle of Bateman had fallen upon Addison's shoulders. He is the only person to have enjoyed the distinction of having three diseases called after him: Addison's anæmia, Addison's disease and Addison's keloid or localized scleroderma. He also gave the first description of xanthoma. During his many years of intimate association with Guy's Hospital he was responsible for building up the unique collection of wax models of skin conditions fashioned by Joseph Towne, the modeller, whom Astley Cooper introduced to Guy's and who served the hospital in this capacity for over fifty years. The famous marble bust of Thomas Addison, which Wilks thought to be such an excellent likeness, is by Towne.

(2) *Addison as Diagnostician*

Secondly, Addison was outstandingly famous as a diagnostician. To him the diagnosis of a patient's illness was a problem that must be solved, however long it took him to do so,

darting from one side of the bed to the other because he was deaf in one ear, and however much he might weary the patient or his student audience in the process. He had been known to return to the Hospital in the middle of the night, much to the astonishment of the ward sister, because just as he had got into bed he realized that he had forgotten to examine a patient he had seen in the afternoon, for a hernia. He was insistent on detailed and accurate recording of clinical observations, and introduced the systematic writing of ward clerk's reports at Guy's. He spent many hours in the dead house, trying to unravel the cause of death in some case the diagnosis of which had eluded him; and it must be remembered that in these days post-mortem examinations were the exception rather than the rule. His fame as a diagnostician made him one of the first "consulting physicians" as we understand the term to-day. The fashionable Victorian physician seldom had cases referred to him by a general practitioner or a colleague. His practice depended on the extent to which he was known to the public, and patients would call at his house and be herded into his waiting room on the off-chance of his being able to see them. Many fashionable physicians such as Gull resigned their hospital appointments comparatively early in life in order to devote more time to the profitable pursuit of their private practices. Gull, for instance, died worth £344,000.

Addison was not a physician of this type. He spent a considerable proportion of his time in the hospital, and though he was a man of forceful personality, who commanded the loyal and devoted respect of his students, he did not always completely satisfy the patient or his relatives, for he was too honest to think much about treatment, which at that time was practically non-existent. Nevertheless his opinion on diagnosis was sought constantly by his colleagues.

(3) *Addison in* 1849 *and* 1855

Addison's discovery was not due to the intuitive brilliance of youthful genius, but rather to the rigid discipline of the trained and mature observer. The monograph of 1855 was the last of his publications, and it is probable that neither he nor his most intimate friends appreciated that it would in time become one of the most famous contributions to medical literature. Indeed it is clear that his brief communication in 1849 to the South London Medical Society was made with diffidence, and would quite possibly never have been made at all but for John Hilton, his surgical colleague, and author of that great surgical classic "Rest and Pain". Addison allowed six years to elapse before elaborating the subject of his modest and unpretentious communication, and there seems little doubt that he would never have written the monograph, but for the diligent preparation of the material and the loyal, and diplomatic, encouragement of his friends and especially of a young man named Samuel Wilks, not yet on the Staff of Guy's.

Addison was anything but a prolific writer, and considering that he was the first to teach the clinical signs of fatty liver, to describe the symptoms and pathology of appendicitis, to demonstrate that pneumonia is due to an inflammatory exudate into the alveoli and not into the non-existent parenchyma of the lung, to demonstrate that phthisis is a mixed infection, that xanthoma is associated with jaundice, as well as describing pernicious anæmia and Addison's disease, the 13 papers which were collected together by Wilks and Daldy for publication by the New Sydenham Society, indicate a degree of literary restraint which might well be emulated by many less eminent and originally-minded writers.

Addison therefore was an old rather than a young man when he wrote his famous monograph. He was in fact 60, and Senior Physician to Guy's Hospital. His influence in the Hospital at this time was greater than that of any Guy's man, including Richard Bright, and except possibly Astley Cooper. He had always been a brilliant teacher. In his early days at Guy's he had earned £800 a year teaching students outside the Hospital Materia Medica. Sir William Hale-White, whose "Materia Medica" is still one of the most authoritative books on the subject, says: "He even made the dry bones of Materia Medica attractive."

He had devoted literally his entire life for the past thirty years to Guy's and the advancement of medicine. He was a bachelor up to the age of 52, and he had no hobbies or recreations, other than an annual visit to Lanercost in Cumberland from which his yeoman ancestry was derived.

Indeed his single-minded devotion to Guy's, his introspective and melancholic nature, and his extreme embarrassment when called upon to speak in public—he confessed that he used to shake with fright whenever he addressed the Guy's Physical Society, a mere student organization—prevented him from acquiring the marks of distinction which his more extroverted colleagues collected with ease. He was never President of the Royal College of Physicians; he was neither knighted nor did he become a baronet, like Gull, or Wilks after him, and Astley Cooper before him; he was not elected a Fellow of the Royal Society. He did, however, become President of the Medico-Chirurgical Society—now the Royal Society of Medicine.

His introspective and melancholic nature was the secret cross he had to bear. He did his

best to overcome it. Wilks, who knew him best, says he was an affable man. His students feared him, respected him and loved him. When he resigned from Guy's they asked him to come back, though he was 65 at that time. The last letter he ever wrote shows how much he appreciated their affection. "I can truly affirm", it says, "that I ever found my best support and encouragement in the generous gratitude and affectionate attachment, as well as my proudest reflections, in the honorable and most exemplary conduct of my pupils." He had been subject to fits of profound depression all his life. They had led him to rise from his bed of insomnia and pace the streets, where he occasionally met some colleague hastening home from a late call. To those who did not know him, these nocturnal pacings would be wrongly construed, and it was whispered that he sought the company of the ladies of the street. On many occasions he had contemplated suicide. In 1860 he retired from public life and from his beloved Guy's, because he thought his younger colleagues and particularly William Gull wanted to deprive him of his position. He went to live in Brighton and, though constantly guarded by two attendants, he succeeded in evading them and threw himself out of a window, to end a selfless though highly introspective life.

The Influence of "King" Harrison on Addison's Career

To turn for a moment to his early life. His appointment to the Staff of Guy's was yet another indication of the prescience of that autocratic personality who was one of the three men who have made Guy's Hospital. The first was Thomas Guy, a governor of St. Thomas's who saw the need to establish a hospital to care for the chronic sick and the insane. The last was Lord Nuffield, whose remarkable benefactions not only to Guy's but to Medicine as a whole have led us at Guy's to erect a statue to his honour during his lifetime. The third man was Benjamin Harrison, Treasurer of the hospital for fifty-one years, from 1797–1848. He was personally responsible for the appointment to the Hospital of Astley Cooper, Richard Bright, Thomas Addison, William Gull and Thomas Hodgkin. The case of Addison is especially noteworthy. Addison had obtained his M.D. in Edinburgh, and he came to Guy's five years later in 1820 as an ordinary student, but owing to the preferment exercised by "King" Harrison he was appointed to the staff in 1824. His only serious rival was Dr. Edward Seymour who had actually received a recommendation to the Governors from the future King William IV.

The Immediate Consequences of Addison's Monograph

In his communication to the South London Medical Society Addison was obviously describing pernicious anæmia, though some of the cases on which this paper was based were examples of Addison's disease. In the 1855 monograph, Addison had not altogether shed the idea of "idiopathic" anæmia, and had yet, on the other hand, gone too far by including cases of malignant disease of the adrenal glands. No one could easily mistake to-day, however, the classical description which he applied to the clinical condition which we now know as Addison's disease.

The monograph was not universally hailed with acclamation. Even twenty years later when Greenhow delivered his Croonian Lectures on Addison's disease he perceived a disinclination to accept the condition as a clinical entity. Papers were written in Germany and France in disproof of its existence. In England specimens were exhibited for years at the Societies, and discussions took place upon them before doubts ceased to be thrown upon the reality of the condition. Two or three papers read before the Medico-Chirurgical Society (now our Royal Society of Medicine) were not approved for publication, so that no record can be found in the *Transactions* of this remarkable discovery. Addison was deeply hurt at this as he had not long before been President of the Society. At Edinburgh, where Addison had obtained his M.D., Hughes Bennett and other professors would not acknowledge the disease. But in Paris, Trousseau gave the condition Addison's name, and Brown-Séquard founded experimental endocrinology after reading Addison's monograph.

In England, however, Addison had one or two staunch supporters. Jonathan Hutchinson reported further cases with post-mortem findings, and Samuel Wilks loyally unravelled the misunderstandings concerning idiopathic anæmia and Addison's disease.

Oliver Wendell Holmes, in "The Poet at the Breakfast Table" describes the following conversation between the poet and Dr. Franklin, whom he consults on account of a discoloration on the forehead.

' "The colour reminds me", said Dr. Franklin, "of what I have seen in a case of Addison's disease, Morbus Addisonii."

I said I thought the author of the *Spectator* was afflicted with a dropsy to which persons of sedentary and bibacious habits are liable.

"The author of the *Spectator*!" cried out Dr. Franklin; "I mean the celebrated Dr. Addison, the inventor, I would say, discoverer of the wonderful new disease called after him."

"And what may this valuable invention or discovery consist in?" I asked, for I was anxious to know the nature of the gift which this benefactor of the race had bestowed upon us.

"A most interesting affection, and rare too. Allow me to look closely at that discoloration once more for a moment. *Cutis aenea*—bronze skin they call it sometimes—extraordinary pigmentation; a little more to the light if you please. Ah! now I get the bronze-colouring admirably, beautifully. Would you have any objection to showing your case to the societies of medical improvement and medical observation?"

"May I ask if any vital organ is commonly involved in this interesting complaint?" I said faintly.

"Well sir", the young doctor replied, "there is an organ which is—sometimes—a little—touched I may say; a very curious and—ingenious little organ or pair of organs. Did you ever hear of the *capsulæ suprarenales*?"

"No", said I, "is it a mortal complaint?" getting nervous.

"It isn't a complaint—I mean they are not a complaint; they are two small organs, as I said, inside of you, and nobody knows what is the use of them. The most curious thing is, that when anything is the matter with them, you turn of the colour of bronze. After all I didn't mean to say I believed it Morbus Addisonii; I only thought of that when I saw the discoloration."

So he gave me a recipe which I took care to put where it could do no hurt to anybody, and I paid him his fee (which he took with the air of a man in the receipt of a great income), and said good morning.'

Comparison Between the Discovery of Addison's Disease, Gull's Disease and Cushing's Syndrome

It has always seemed to me interesting to compare the circumstances under which Addison's disease, Gull's disease and Cushing's syndrome were launched upon the medical profession.

Addison, a morose and parochial physician diffidently describing first pernicious anæmia, and then, goaded on to more spectacular publication, produced a monograph which is still a masterpiece of clinical virtuosity, accurate and even now up to date in every detail. This monograph, now one of the most famous in medical literature, was the subject of bitter controversy when it first appeared.

Gull, Napoleonic, epigrammatic extrovert, the "physician of fashion", as he once described himself, of the 1870's, who had lately been called in by Sir William Jenner to attend the Prince of Wales in his attack of typhoid fever, and had won the heartfelt thanks not only of the Nation but also of a mother who had lost her beloved husband from the same complaint: Gull, now Sir William, and one of the most famous men in England, read a paper in 1873 to the Clinical Society of London "On a cretinoid state supervening in adult life in women". The paper was brief and not very different from the usual type of communication that was constantly reported in the *Transactions* at that time. It was, however, by Sir William Gull, and that sufficed to draw attention to it. This paper contained the first description of myxœdema, and though William Ord elaborated the clinical syndrome in 1877 and called it "myxœdema" there was no doubt from the beginning that it was Gull who discovered the condition. It is, however, interesting to note that though it is quite frequently still spoken of on the Continent and in America as "Gull's disease", I found it necessary in announcing the title of a clinical lecture I was to give at Guy's Hospital last year on "Gull's Disease" to add in brackets "Myxœdema".

Cushing's syndrome was described by Harvey Cushing in 1932 in the *Bulletin of the Johns Hopkins Hospital*. He recorded 12 cases of this syndrome, and as he told me himself he travelled sometimes many hundreds of miles at short notice to be present at the post-mortem of some of the cases reported. Once again the eponym was applied by someone in another country (Bishop and Close), this time in England, and in this case it is possible that the eponym is well applied, for we still are not certain where the lesion lies, whether in the basophil cells of the pituitary, in the adrenal cortex, or whether, in some cases, there is a lesion at all. Cushing, at the time of his description of this syndrome, was the most famous neurosurgeon in the world. Whatever he might describe would instantly attract attention.

Cushing's discovery is not so very long ago. We are apt to think that Medicine has become so complicated, and so dependent on the laboratory and on team work, that no one individual can stand out as a giant among his peers in this rapidly progressing subject of endocrinology. This is surely not true. Fuller Albright, for instance, still a young man, is a prodigious giant of clinical and biochemical endocrinology, and it is my belief that the days of discovery of important and exciting syndromes have not yet passed, and that members of

this Section will continue to emulate the brilliant example of Thomas Addison, the founder of endocrinology, a hundred years ago.

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Section of Urology

President—Professor CHARLES WELLS

[*October* 27, 1949]

Studies in Chronic Retention

PRESIDENT'S ADDRESS

By Professor CHARLES WELLS

IN my Unit, we have, for three years, been considering renal function in prostatism and other obstructive states. This is an account of a small group of patients studied in considerable detail over a period of a year, certain of the cases having been followed for a longer period. The labour of research has been borne chiefly by Mr. Raphael Marcus. The operative procedure has, in all cases, been that advocated by Mr. Wilson Hey, with certain minor modifications. No patient has been refused operation, and cases of complete obstruction have been dealt with by immediate prostatectomy without preliminary catheterization. Intravenous pyelography has preceded surgery in all cases.

The smooth convalescence usual after the Wilson Hey procedure has enabled us to make comparable observations in all our cases.

Availing ourselves of the evidence of intravenous pyelography we have for our own purposes classified our cases pre-operatively into:

(1) Those in whom the upper urinary tract is normal, or almost normal.

(2) Those in whom there is a marked degree of hydronephrosis due to back pressure, and

(3) Those in whom there is such back pressure that there is no renal shadow and very little evidence of any excretory activity visible in any part of the urinary tract.

It is surprising that with even the highest degrees of chronic retention we have found a number of cases with completely intact upper urinary tracts.

The following are four striking examples:

CASE I.—W. H. M., aged 72. He reported with his bladder distended to above the umbilicus and he looked gravely ill. His intravenous pyelograms disclosed a normal upper tract.

CASE II, F. R., and CASE III, J. D., were two patients who were catheterized in Canada for the relief of chronic retention which had become complete. They crossed the Atlantic without mishap with catheters tied in and successfully underwent prostatectomy. The anatomy of the upper tract was normal.

CASE IV.—C. C. W., aged 65. This patient was rushed into hospital because of his greatly distended bladder. Intravenous pyelograms showed normal kidneys (*see* Fig. 1 which illustrates this case and is typical also of the other three).

It is of interest that two of these patients actually crossed the Atlantic with catheters tied in the urethra and arrived in this country in perfect condition. I think it is a fair assumption that their easy journey was due to the fact that their kidneys and ureters were intact. Two other assumptions follow. Firstly, that patients fortunate enough to have suffered no renal damage due to back pressure should do well whatever the basis of their operative treatment, and, further, that to subject such patients to a tedious two-stage procedure because the bladder is dilated is unjustifiable and a waste of time.

When the figure is available at the time of pre-operative assessment it will be found that these patients, even with a high degree of bladder distension, mostly have a relatively low blood urea. In the two non-catheterized patients described, the figures were 35 mg.% and 38 mg.%. The condition is a clinical entity which should be carefully considered because of its favourable operative prognosis.

The intermediate group in which there is a moderate degree of back pressure is naturally not easy to define. Amongst the examples which I quote is one which demonstrates that a low blood urea alone is not proof of an intact upper tract.

CASE V.—C. W. H., aged 71, had had overflow incontinence for six weeks. His blood urea was 35 mg.%. Intravenous pyelograms at five minutes revealed no collection of "Pyelectan". At fifteen minutes the dilated calyces were seen and the pyelogram at thirty minutes showed gross hydronephrotic changes and tortuous and dilated ureters (Fig. 2). Figs. 4 and 5 show his progress after operation.

How this change in the upper urinary tract becomes established is a matter about which we have insufficient evidence to be dogmatic. We have attempted a few experiments in producing reflux up the ureters both in man and experimental animals. So far as our evidence goes it suggests that the intact ureter does not allow fluid to be forced up and it suggests further that in the prostatic subject, once the process starts, there is a preliminary period in which the lower ureter only is dilated. We think it likely that once established this progresses relatively quickly to affect the whole ureter, including the renal pelvis, with the production of hydronephrosis. My impression is that blood ureas are normally either below 40, indicating little back pressure, or up to 100 or more, indicating hydronephrosis. Few are caught in between. I am not prepared to place much emphasis upon the significance of the preliminary stage of back pressure change, except in so far as it elucidates the mechanism of production of hydronephrosis and the ascent of infection to the kidney level. Fig. 3 (*a*) (Case VI) shows an example of ureteric reflux and (*b*) the increased back pressure caused by attempting micturition with the urethra clipped.



FIG. 1 (*Case* IV).—C. C. W., aged 65. Note bladder distended to level of interspace L 3/4 with anatomically normal ureters and kidneys.



FIG. 2 (*Case* V).—C. W. H., aged 71. Gross dilatation of the upper tract associated with chronic retention due to enlargement of the prostate. Film at thirty minutes after injection of dye.

Altogether there have been amongst our cases, during the relevant year of research, 28 with such a degree of residual urine as to qualify for the description of "chronic retention". 80 to 100 ounces of urine have usually been found in the bladder. Of these 28, 5 have fallen into the first category with normal pyelograms, 16 into the second with dilated pelves, and 7 into the third with no demonstrable function. Every case has been subjected to operation, 9 as emergencies[1] without previous investigation, other than intravenous pyelography, and 19 as elective procedures. Of 18 consecutive cases operated upon by me personally none has died. (One other prostatectomy, a known carcinoma who had failed to respond to stilbœstrol, did die. His death was due to dehydration with œdema.) Of the 10 operated upon by others of the team one died. He was too ill to co-operate and could not be got out of bed. He developed hypostatic pneumonia to which he succumbed. He was one of the 7 in the small third group, with no demonstrable function. He should have been refused prostatectomy because of his inability to co-operate (Wells, 1949).

[1] These do not represent all the patients operated upon as emergencies. Simple acute retentions without previous chronic retention are not included in this study.

When we realized what a uniform and smooth convalescence could with confidence be expected in these cases we decided to intensify our investigations during and after the time of operation.

It will serve our purpose best if we turn now to illustrate this by describing in detail one of the patients whose X-ray, Fig. 2, has already been shown above.

C. W. H. (Case V), aged 71, had had overflow incontinence for six weeks. We have already seen in fig. 2 the hydronephrosis present before operation. His blood urea at that time was 35 mg.%. Fig. 4 shows his pyelogram eighteen days after prostatectomy. Fig 5 is one year after operation. His blood urea was then 29 mg.%



FIG. 3A (*Case* VI).—Chronic retention with reflux up the right ureter.

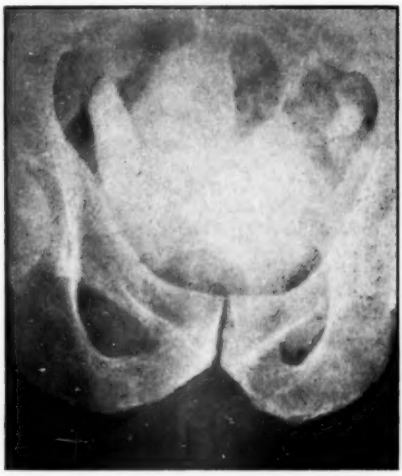


FIG. 3B (*Case* VI).—The same as 3A, taken a few moments later, on attempting to micturate with the urethra clamped. Increased ureteric reflux is demonstrated.



FIG. 4 (*Case* V).—C. W. H., aged 71. Intravenous pyelogram showing improved condition of upper tract eighteen days after operation.

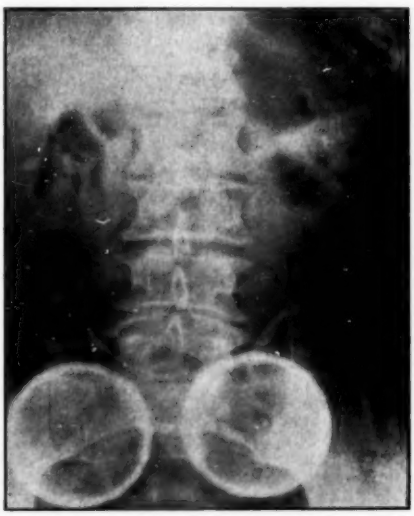


FIG. 5 (*Case* V).—C. W. H., aged 71. I.V.P. Ten minutes after injection of dye one year after prostatectomy.

Probably the most impressive single fact in this case is the amount of recovery which has taken place in the previously dilated upper urinary tract. The blood urea was never seriously raised and fluctuated very little. Although it has come down the change was not great. The change in his general condition has been quite remarkable. At the time of operation there was marked œdema of the legs below the knee, and this cleared rapidly during the first few days. This is a phenomenon which we have observed in a small number of cases. In one in particular (Case VII, G. M., aged 74) both legs were very heavily waterlogged and there was œdema round the pelvis and sacrum. The urinary output, without forcing fluids, during the first few days was as follows: First day – 108 oz., second day – 142 oz., third day – 130 oz. Within one day the œdema of the legs had disappeared. The blood urea was 120 mg.% at operation ; 50 mg.% next morning ; and 45 mg.% forty-eight hours after prostatectomy.

It would appear that in the presence of prostatic obstruction water can be voided from the bladder only at a certain rate and therefore in a certain limited total quantity in the course of twenty-four hours. Any excess of water becomes locked up in the tissues as œdema. The moment the obstruction is released the fluid shifts back from the tissue spaces into the circulation and is voided with a consequent diuresis out of proportion to the fluid taken by mouth.

The very striking change in the pyelograms in the case I have just described is characteristic of the patients in whom there is demonstrable function with some back pressure.

In Case VIII (Mr. D., aged 68) Fig. 6 shows the condition before operation (A) and ten days after operation (B). Case IX (Mr. L.) had a large diverticulum which we were able to remove cleanly and completely.

The opportunity to do this at a first-stage operation is a great advantage, since the diverticulum becomes gravely infected in the course of catheter or suprapubic drainage. Once infected, its removal is fraught with difficulty and, indeed, with danger.

One of the most striking examples of rapid recovery of renal and ureteric anatomy is instanced in Case X, K. W. P. (Fig. 7 A and B). The very considerable degree of improvement within a period of five weeks in this case is most striking. Another feature of the case, however, points an even more important lesson. During his convalescence he developed a severe urinary infection with *Bacillus pyocyaneus*. In the presence of dilated ureters this infection ascended rapidly to the kidney level and with a sharp rise in temperature he became oliguric and then virtually anuric. His blood urea rose from 40 to 120 mg.%. The organism was tested for streptomycin sensitivity and a course of that antibiotic immediately instituted. At the end of the first six-hour period the urine was almost sterile and after each of the two ensuing six-hour periods it was completely sterile. Concurrently with this bacteriological improvement the general condition became better, and the excretion of urine was resumed. The infection relapsed after the withdrawal of streptomycin but not at the kidney level, and there was no further check to the excretion of urine.

Here was a clear example of surgical kidney. The advent of pyelonephritis was associated with depression of renal function and in the old days would have proved fatal. Not only does the case illustrate the value of streptomycin in relieving this previously fatal condition, but it also suggests strongly that failure of renal function is not due to rapid decompression but to the introduction of sepsis. Amongst the cases which we have observed in our own service and that of others, we have seen a number of other examples of patients in a precarious state with mounting blood urea and diminished urinary output associated with infection. In every instance the fact that the failure of renal function was due to infection has been made immediately clear by the rapid response to streptomycin. In some instances where preliminary drainage had been instituted, the improvement after streptomycin enabled the surgeon to proceed at once, and successfully, to the prostatectomy at which he had baulked in the beginning when the case was uninfected. (When sepsis has been checked with streptomycin it may be necessary to act quickly before a relapse occurs.)

It is not my purpose to discuss the merits of streptomycin in the management of urinary sepsis, but to demonstrate how the control of infection is followed by a return of renal function.

Here is a further example:

Case XI.—T. C. W., aged 68. This patient was admitted with retention of urine and cystitis following previous catheterization. His blood urea was 42 mg.% and culture of urine grew *Staph. aureus*.

20.6.48: Prostatectomy with closure of bladder.

28.6.48: Blood urea 107 mg.%. Culture of urine—*B. pyocyaneus* and *B. proteus*. Colonies too numerous to count. Both organisms inhibited by streptomycin, 32 units per millilitre.

29.6.48: Patient's condition deteriorating. Rigors and anuria. Streptomycin treatment commenced.

30.6.48: Culture of urine sterile. Blood urea 228 mg.%.

7.7.48: Blood urea 57 mg.%. Condition much improved.

18.11.48: Sterility of urine maintained. Blood urea 33 mg.%.

The next feature to which I wish to draw attention is the change in blood-urea figures after the relief of prostatic obstruction, and more particularly the rate at which that change occurs. Up to a few years ago I had always imagined that blood urea moved rather slowly and that under catheter or suprapubic drainage it was desirable to take readings at intervals of about a week. I imagined that by comparing these readings one could construct a graph which would show roughly the improvement in the case under consideration. It is now apparent that such a conception is quite valueless. Blood-urea levels change not from week to week, nor yet from day to day, but from hour to hour. In order to obtain a true picture of the relief of azotæmia following the relief of obstruction it is necessary to take very frequent readings. I have already quoted one example (Case VII, G. M.).



FIG. 6A (*Case* VIII).—Mr. D., aged 68. Condition of upper tract before prostatectomy.

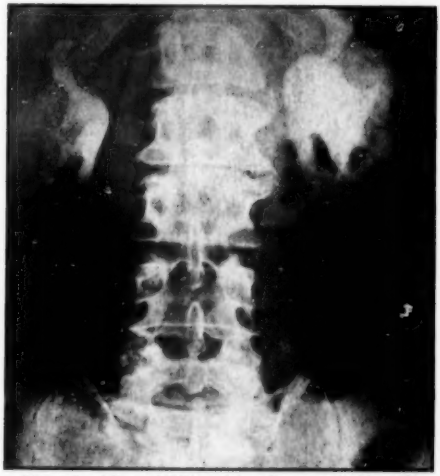


FIG. 6B (*Case* VIII).—Mr. D., aged 68. The same case ten days after operation.



FIG. 7A (*Case* X).—K. W. P., aged 57. I.V.P. at thirty minutes after injection, before prostatectomy.

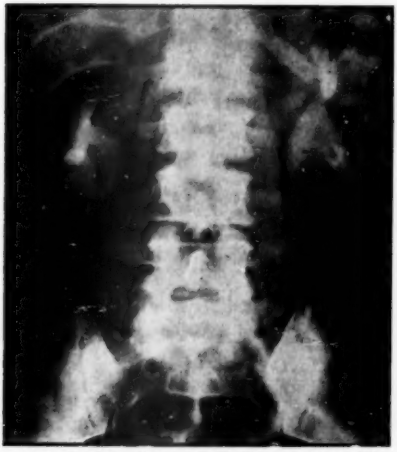


FIG. 7B (*Case* X).—K. W. P., aged 57. The same as 7A. Five weeks after operation.

I cannot better illustrate my point than by describing 3 of the most advanced cases of chronic retention with which we have dealt.

CASE XII.—C. W., aged 63, had had slight nocturnal incontinence for four years. His general condition was poor with urinary urea 0·9 grammes %, and blood urea 115 mg.%. The day after prostatectomy the blood urea rose to 150 mg.%. The following day it was back to 115 and the day after that down to 90 mg.%. One year after the operation the blood urea was stable at 57 mg.%, the urinary urea was unchanged and the kidneys just visible in i.v.p.

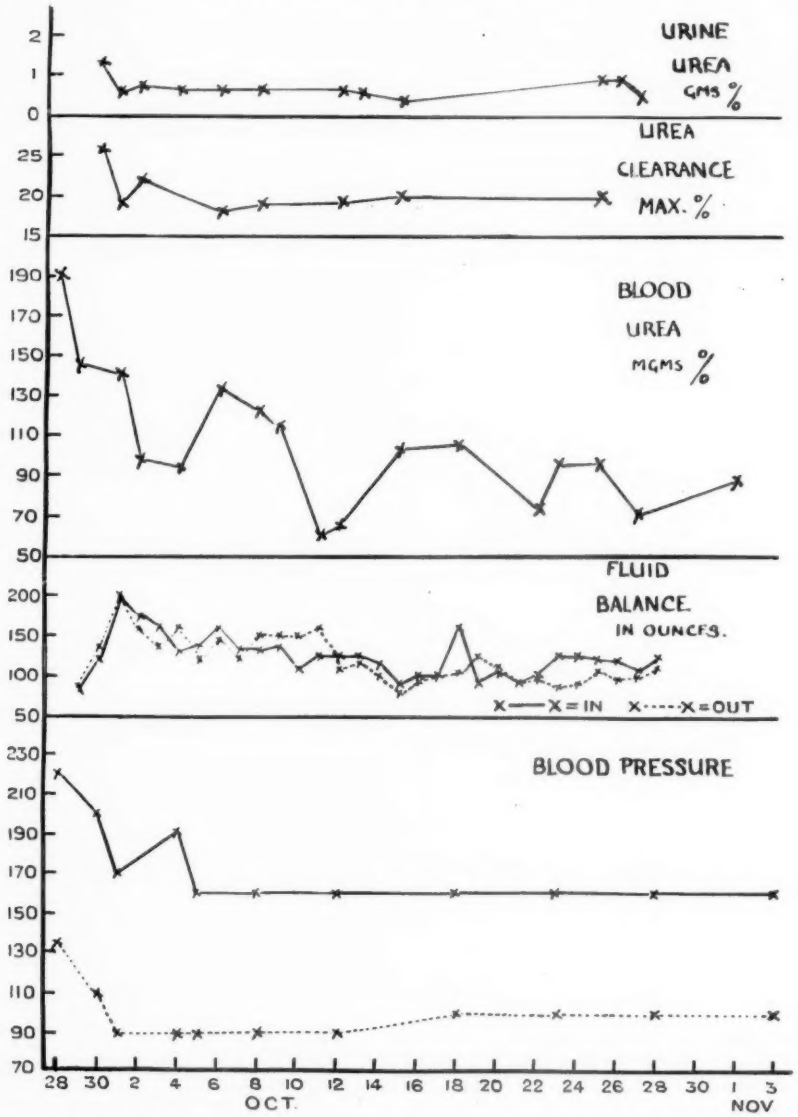


TABLE A (*Case* XIII).—J. B. N., aged 64. Note the rapid rate of fall of blood urea during the first forty-eight hours in association with forced fluids and free diuresis. The percentage urea in the urine remains steady throughout. This patient was able for discharge fourteen days after prostatectomy but was retained for further observations to be made.

CASE XIII.—J. B. N., aged 64, had had overflow incontinence and uræmic dyspepsia for one year. Before operation his blood urea was 190 mg.%, and the intravenous pyelogram showed no function at all. Prostatectomy was performed and the next day the blood urea was 146 mg.%. One year after prostatectomy the blood urea is stable at 100 mg.% with urinary urea 0·7 gramme%; no residual urine but a mild persistent *B. coli* infection. Almost nothing is visible in the i.v.p. but the patient is well and working (*see* Table A).

CASE XIV.—E. J. E., aged 78, had had overflow incontinence and generalized œdema for nine months. Vitamin-C deficiency and senile Parkinsonian tremor were manifest. Blood-urea levels immediately before and after prostatectomy (i.e. at an interval of only two hours) were 160 and 130 mg.% respectively. The intravenous pyelogram before operation showed no function. There was a greater urinary output than fluid intake in the post-operative period, the œdema disappearing rapidly. Six months after operation the blood urea was still 105 mg.%, but improved to 72 mg.% on increasing the daily fluid intake by three pints. There was a persistent infection with *B. pyocyaneus* (*see* Table B).

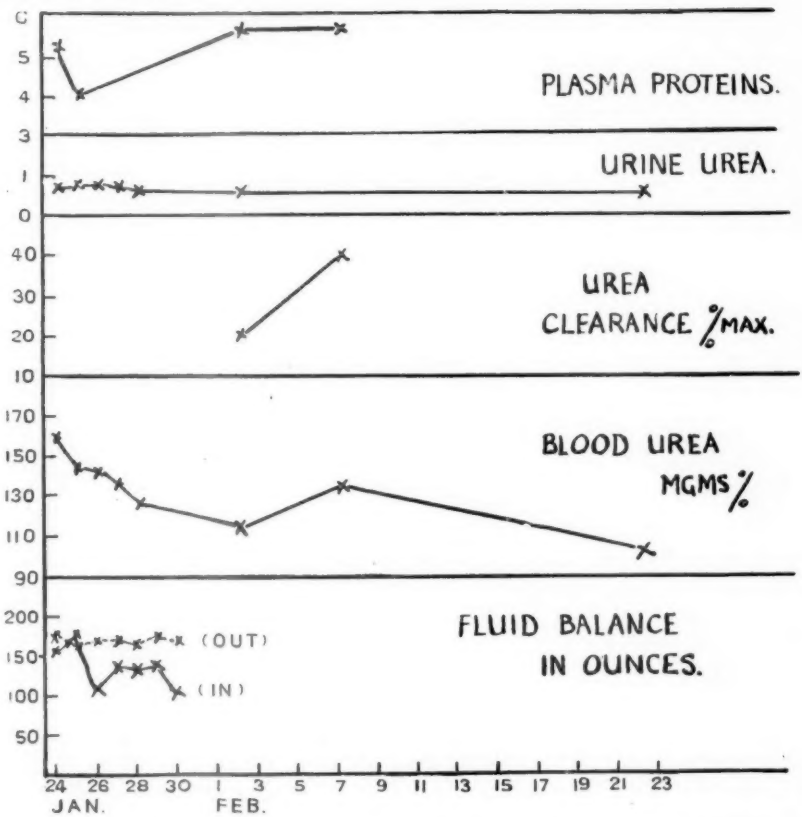


TABLE B (*Case* XIV).—E. J. E., aged 78. Note the rapid fall of blood urea in the first few days with free diuresis in marked excess over the fluid intake but associated with rapid disappearance of œdema.

It is important to realize that in these cases the improvement in the blood-urea levels, that is the relief of azotæmia, is due not to an improvement in renal function so much as to the fact that the urine can be got away. Once the obstruction is relieved it is possible to pass water through the kidneys almost as though they were simple dialysing membranes. The level of urinary urea does not rise during the period of observation. The clearance of waste products from the blood is effected by heavy diuresis.

The sensitivity of blood-urea readings to variations of fluid intake was well illustrated in a patient who had a nephrectomy for tuberculosis. The remaining ureter became obstructed and the ureterostomy was needed as a life-saving measure. This gave relief

only so long as a copious fluid intake was maintained. Shortening of the fluid intake was reflected within a few hours by a sharp rise in the blood urea.

The extent to which this diuresis needs to be pushed in prostatism has not been sufficiently realized hitherto. Once the obstruction has been relieved, provided the patient is not suffering from chronic interstitial nephritis, and provided that he has not got pyelonephritis, fluids can be given in almost unlimited quantities without any danger of drowning.

The amount of fluid required during the first few days in order to ensure a rapidly and steadily falling blood-urea level is so great that it cannot possibly all be taken by mouth, and intravenous therapy is an essential part of the management of these very severely damaged cases. Ten and eleven pints of fluid in twenty-four hours are the highest figures which we have hitherto given and it has been remarkable in the cases in which these large quantities have been prescribed to observe a fading away of existing œdema rather than an appearance of new œdema.

On the question of electrolyte balance, I will merely say that there is a risk both of giving too much sodium chloride and of giving too little sodium chloride. If too little is given a state of alkalosis appears and urea is retained in the circulation. If too much sodium chloride is given the kidney is unable to get rid of it, and large quantities of fluid are retained in the body as œdema in order to look after the excess of salt. It is indeed possible in these cases, we believe, to have œdema of the intercellular tissues with an excess of chloride, and at the same time to have dehydration of the cellular organs. This state of affairs exists because the total electrolyte content of the cell is stable and in order to remain in something like isotonicity with the surrounding tissues the cell has to give up fluid. (Compare the crenation of red blood cells when placed in hypertonic saline.) The clinical picture of this state is one of œdema with a dry rough skin and a dry mouth. In spite of the presence of œdema these patients are in urgent need of fluid which should be given in the form of 5 or 6% glucose. Another thing to remember is that in the presence of very heavy diuresis chlorides may be excreted from the body in large quantities. It is necessary, therefore, in the management of these patients to keep an eye upon the chloride level and this is most easily done by estimating the amount coming away in the urine by the simple drop technique of Fantus (1936.)

If the chloride situation is satisfactory, the governing factor in the amount of fluid required is the percentage of urea found in the urine. A simple mathematical equation will enable one to estimate the volume of urinary output required to get rid of the daily intake of protein, and at the same time to carry off a portion of the accumulated excess of nitrogenous waste products.

I have discussed three cardinal points in the maintenance of good renal function, namely the relief of obstruction, the control of infection and the supply of adequate fluid. There is one other factor of great importance. The blood supply to the kidney must be maintained at an adequate pressure. We have long suspected that a severe fall of blood pressure associated with the operation may interrupt the output of urine and that its re-establishment may take an appreciable time which the uræmic patient cannot afford. Whether or not this is true, we can at least demonstrate the effect of careful blood-pressure control during and after the operation.

Our anæsthetic technique is based on the desirability, indeed the absolute necessity as we think, for maintaining an even blood-pressure level. We do this by means of a continuous intravenous drip containing adrenaline in a solution of 1/250,000. By adjusting the rate of the drip it is possible to control the systolic blood pressure with a very considerable degree of nicety (*see Brit. J. Anaes.*, 1949, **21**, 182). Using this technique we have again and again demonstrated the continued excretion of indigo-carmine from the kidney during the operative procedure. In a series of 20 cases, there was little or no difference in the time taken for excretion of dye during operation, compared with the intervals observed before and after operation.

Since using this technique we have similarly observed repeatedly the output of very large quantities of water in the hours immediately following the operative interference. We have demonstrated that with careful management renal function is not interrupted by the operation and this is constantly reflected in the immediate post-operative fall in blood-urea levels when previously raised and the absence of any rise when previously normal.

The anæsthetist gives a spinal anæsthetic and in addition we like our patients to be asleep with a little pentothal. I have no doubt that there are other satisfactory anæsthetic combinations, but by employing the means I have described, viz. pentothal, spinal and adrenaline, we ensure a number of desiderata:

(1) We get complete relaxation. The spinal anæsthetic is controlled so as to extend to about the level of the umbilicus.

(2) We get a peaceful patient who is not worried by the operative procedure.
(3) We get a relatively dry field in spite of maintenance of a steady blood-pressure level.
(4) We have an anæsthetic which, once given, lasts for a couple of hours so that there is no need to hurry the operation and nothing to be gained by getting away quickly.
(5) The patient recovers consciousness and recovers the use of his legs in an orderly and gradual fashion with the minimum of excitability and post-operative disturbance.

What I have said really completes my case. We began this work with a view to finding out what happens in the patient with chronic retention who has his prostate removed. We started with certain preconceived notions which we were anxious to test. Our theories were:

(1) That renal failure due to obstruction could best be relieved by immediate and complete removal of that obstruction. All our observations have confirmed this belief. Incidentally, on opening the bladder we have often seen a deep flush over its whole surface and a readiness to bleed from the surface of the prostate. We have often seen fountains of water coming down the ureters, but we have never seen any blood come down them.

(2) That interruption of the favourable course of events after the relief of obstruction is due to some intervening cause of which sepsis is the most probable. This is a somewhat difficult thesis to substantiate beyond all question, but our experience with streptomycin in ascending pyelonephritis has satisfied us of the validity of the contention. An episode of low blood pressure is the second most probable cause.

(3) That given a known level of urinary urea and blood urea it should be possible to estimate the amount of fluid necessary to produce a steady improvement in the level of waste products in the blood. This we have found to be the case, and in studying this notion we have learned a great deal about the sort of care it is necessary to take in the management of the balance of fluid in these patients.

Certain other interesting points have emerged from our studies. We have now followed some of these patients for about two years. We have observed the steady improvement in their general condition and we have taken repeated samples of urine and repeated readings of blood pressure. We have satisfied ourselves that rapid and valuable recovery of renal function is possible in patients whom we would include in our middle group. It seems equally clear that those falling into the third group never recover concentrating power and depend entirely upon free diuresis for the adequate clearance of waste products from the blood-stream. In these cases, high blood-urea levels may persist for many months, but are compatible with a comfortable and useful life.

The urinary samples show us that the patients who leave hospital with a sterile urine remain sterile. Of the remainder who leave with infection, the infection persists in 4 out of 5 cases. In one case we have observed infection cause a gradual deterioration ending in death from insidious ascending urinary sepsis at the end of about a year. We think it probable that patients who show persistent sepsis three months or even less after prostatectomy should be readmitted to hospital, fully investigated, and subsequently treated by every known means with a view to clearing their urine.

In passing, and in regard to sepsis, we have reviewed our notes in order to clear up a point of doubt which is repeatedly arising in conversation, namely whether the patient with chronic retention is likely to have a sterile or an infected urine. A review of our cases has confirmed our contention that with very few exceptions the urine is sterile in chronic retention and in prostatics generally, unless there has been previous instrumentation. In relation to this point I would point out that we have not refused operative interference in any of our cases on account of previous catheterization although we deplore it and think it should be avoided whenever possible. The previously catheterized patients have certainly given us more trouble than the others. In this connexion I might mention the post-mortem findings in a patient with severe chronic retention who was cystoscoped for diagnostic purposes: he died from pyelonephritis within a few days of this simple examination. We have, during the period under review, seen more than one other case in which catheterization in chronic retention without any further interference has led to a fatal issue. It is our belief that these simple procedures are dangerous for the reason that the obstruction to the neck of the bladder is not removed and recurrence of retention with massive reflux up the ureters is a very likely sequel.

These last observations I have made as a reminder that the more conservative approach to these cases is not itself without danger. I am, however, fully aware that if the same rules of management which I have described are applied we may hope to see equally favourable improvements in the upper urinary tract following the relief of obstruction by other techniques than those I have described and with different timing. My purpose was not to discuss the technique of the operation, nor even to debate the relative merits of single versus staged procedures, but to describe the changes which ensue when obstruction has been relieved.

My last word but one has to do with blood-pressure levels. I came to this work with a preconceived notion that in chronic retention the blood pressure was raised and that following its relief the tendency was for the blood pressure to fall to a lower level. In the cases under review the results have been so capricious that I now feel at a loss to predict the change likely to occur. For every two that have gone down, one has gone up to a higher level (Table C).

TABLE C

		Blood pressure in mm.Hg		
No.*	Name	Before operation	On discharge or one month after operation	Six to eighteen months after operation
1	J. G. F.	120/80	180/90	220/120
2	J. B. N.	220/135	170/100	170/110
3	C. W.	230/130	140/85	170/100
4	J. W. B.	120/80	110/75	170/110
5	W. E. K.	200/100	170/90	250/90
6	K. W. P.	130/100	110/75	160/90
7	A. W. D.	150/70	120/80	150/80
8	E. T.	190/90	160/90	170/90
9	B. C.	140/80	120/80	160/70
10	L. W. D.	215/110	190/110	190/110
11	M. M.	220/110	190/100	190/110
12	J. J.	145/80	130/80	130/90
13	W. S.	170/110	140/100	200/120
14	C. W. H.	200/90	160/80	180/90
15	Mr. L.	170/100	120/70	140/80
16	C. C. W.	160/110	160/110	200/110
17	T. B.	260/145	200/120	Died
18	E. J. E.	240/130	200/110	220/90
19	H. O.	190/100	135/90	170/100
20	J. F.	200/100	180/90	140/90
21	J. M.	165/90	Died	—

* The case numbers in this Table do *not* accord with those given elsewhere in the text.

I must finish by sounding a note of warning for any who may feel disposed to take a more radical approach towards their prostatic problems. I believe there is one contra-indication which is likely to defeat the surgeon no matter what technique he employs. I speak of the arteriosclerotic patient who is incapable of co-operation. Any procedure which involves post-operative apparatus of any kind is likely to get us into trouble with cases of this character, and so far no one has devised any operation for the prostatic patient which does not involve some sort of apparatus. Probably transurethral resection most nearly approaches this ideal

Whatever is done, the operation is only a step in treatment. After-care, immediate and remote, is all-important and there is no field of work in which close attention to detail will prove more rewarding. Many workers such as Cook, Creevy, Lane, and D. K. Rose have kicked against the bogey of slow decompression. Wilson Hey has provoked us to further thought and further enquiry. I hope the studies here presented will be adjudged a useful and objective contribution.

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Modern Drugs in Dental Surgery

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IN order to review and assess adequately the values of modern drugs which have proved useful in dental surgery, it would be desirable to compare their efficiency with that of drugs formerly used for similar purposes. It would be impossible to do this in a short paper and even individual knowledge and experience would inevitably be called in question. It would be advantageous if concerted British dental authority could be obtained to jettison the useless or less efficient drugs in order to concentrate attention and critical clinical observation upon the more valuable dental medicaments. Such a selection of useful drugs for dental surgery should be based upon known pharmacological actions and practical clinical experience which do not always coincide. In making this plea, I include the necessity for a review of the many proprietary preparations which are provided sometimes for convenience in use and sometimes on dubious pharmacological grounds. Some thirteen years ago I condemned arsenic as a devitalizing agent and this produced private and public letters denouncing my ignorance ; yet I had suffered from its use personally three times. Again, iodoform still persists as an antiseptic ingredient of mummifying pastes and root-canal fillings, but upon no sound pharmacological foundation.

DENTAL ANTISEPTICS

At present, about 60 prevalent antiseptics would have to come under review, some prevalent merely because of attractive advertising. A generally useful series of dental antiseptics would doubtless include: hydrogen and zinc peroxides, sodium hypochlorite, iodine, formaldehyde and paraform, zinc sulphate, alcohol, phenol, cresol and a chlorocresol or chloroxylenol, clove oil, thymol, one surface-reducing agent, proflavine, gentian violet, sulpha drugs, penicillin and streptomycin.

Two recent additions to the *peroxides* merit comment. Zinc peroxide, a mixture of ZnO_2 (45%) with ZnO and Zn $(OH)_2$, evolves oxygen and leaves a residue of zinc hydroxide, which has useful antacid and astringent properties. Zinc peroxide, in powder, has proved a valuable application against anaerobic organisms in diabetic gangrene and as a paste in anaerobic gingival infections. Sodium percarbonate, Na_2CO_3, $1\frac{1}{2}H_2O_2$, on the other hand, leaves, on evolving its oxygen, the highly alkaline carbonate and from experimental tests by Dr. J. B. Roberts, in my department, it is unlikely to displace the less alkaline sodium perborate.

The detergent and antiseptic action of *surface-tension reducing agents*, such as hard soap is familiarly used in dentifrices, but fresh interest was aroused in this group by the slightly higher bactericidal efficiency and greater stability of *sodium ricinoleate* solutions which have a general, although not a specific, antiseptic applicability. Similarly irium, which is sodium lauryl sulphate, is another anionic detergent which has been much vaunted as an antiseptic in a dentifrice. It inhibits the Gram-positive, but not materially the Gram-negative, bacteria. It has the practical advantage for chalky districts that its calcium and magnesium salts are soluble, hence, added to ordinary soap, it retards the formation of insoluble calcium soaps. *Liquor sulphestolis*, or teepol, a solution of sodium secondary alkyl sulphates, has similar properties, and is effective in 0·5% solutions for cleansing surgical instruments.

Cetrimide, or *cetavlon*, is a cationic surface-reducing and bacteriostatic agent, consisting chiefly of trimethyl-cetyl-ammonium bromide, $C_{16}H_{33}(CH_3)_3N.Br$; it is not irritant or toxic to raw or mucous surfaces. It is highly effective in 1% aqueous solutions as a pre-operative detergent and antiseptic for the skin and wounds because the bacteriostatic effect lasts on the skin for some hours after it has dried. It is also useful for sterilizing instruments if 0·2% sodium nitrite is added to prevent rusting.

The *acridine dyes* are the most effective antiseptics against Gram-negative organisms; four are now available—acriflavine, proflavine hemisulphate or monohydrochloride, aminacrine hydrochloride and euflavine. For wounds, 0·1% solutions are used but, with prolonged use, they tend to delay healing. For oral infections 0·1% up to 1% aqueous, alcoholic or glycerin solutions are suitable as paints. Proflavine hemisulphate is most frequently used but aminacrine hydrochloride is less irritating, less staining and rather more efficient; these form neutral solutions (pH6) whereas that of acriflavine is acid (pH2).

Crystal or *gentian violet* (*Viola crystallina*) and *brilliant green* (*Viride nitens*), in 1% solutions as paints, have an effective toxicity for Gram-positive organisms, especially streptococci and staphylococci, and for the Gram-negative *Pseudomonas aeruginosa* (*Ps. pyocyanea*). Crystal violet is generally preferred and the tough superficial film which it forms is more resistant to bacterial invasion than that of tannic acid. The statement that it inhibits *Monilia* (*Candida*) *albicans* has been questioned by Seltzer and Bender (1949) who believe that 0·1% aqueous iodine is the only effective drug clinically for Monilia infections.

Ammonium and Urea Salts

Amongst recent remedies, mention should be made of the advocacy of ammonium salts with urea as oral antiseptics. The Groves (1934, 1935, 1942) announced that weak ammoniacal solutions had a solvent effect on mucin and plaques and reduced caries activity.

Kesel (1946–49) found that Lactobacilli disappeared from glucose cultures containing saliva from caries-immune cases and that the inhibitory substance was ammonia, possibly formed by antagonistic bacteria partly from urea and partly from breakdown of amino acids. Dibasic ammonium phosphate in 5% solution was considered a suitable ammonium salt to reduce the oral Lactobacilli and to be more efficient in the presence of urea. Urea it may be noted, is known to be a peptizing agent and a solvent of necrotic tissue, and it enhances the antiseptic action of sulphonamides and penicillin.

Henschel and Lieber (1949) evolved a dentifrice containing dibasic ammonium phosphate 5%, urea 22·5%, bentonite 5%, sodium lauryl sulphoacetate 3%, volatile oils 1%, saccharin sodium 0·3%, and precipitated calcium carbonate 63·2%, and they believe that it acts "by virtue of the protein denaturing action of the urea which combined with the ammonium phosphate produces a strong buffering action at the site of acid formation."

But this shotgun dentifrice does not lend itself to scientific assessment : Bentonite is a colloidal hydrated aluminium silicate which forms a colloidal gel and may have some adsorptive effect; the sodium lauryl sulpho-acetate is a surface-tension reducing antiseptic; and the volatile oils are also antiseptic.

While indicating a reduction of caries incidence by its use, Henschel and Lieber admit that some proportion of this may be attributed to enthusiastic use of the new dentifrice. The available clinical evidence is not convincing; and it may be recalled that Bruckner (1948) found that sodium bicarbonate as a dentifrice would lower the oral lactobacillary content.

Sulphonamides

The sulphonamides as bacteriostatic agents for oral infections have several defects. Their activity is impaired by pus, bacterial debris and products of tissue autolysis and also by substances containing *p*-amino-benzoic acid such as procaine, butacaine, benzocaine and orthocaine; further, the fact that, in order to displace *p*-amino-benzoic acid, they have to be maintained in considerable excess locally militates against their general utility for oral infections. They are bacteriostatic for Gram-positive organisms, hence for mixed infections S.P. powders (sulphathiazole 99%, proflavine 1%) are commonly used, or penicillin-sulphonamide powders (15,000 units per gramme of sulphathiazole): these are useful local applications in osteomyelitis, as adjuvants to surgical treatment and systemic bacteriostatic agents.

The earlier claims made for sulphonamides in Vincent's and other parodontal infections were unwarranted, and even sulphathiazole chewing gum, containing 0·25 gramme, has been shown to reduce chiefly the streptococcal flora of the mouth (Lewis and Burket, 1948). When, however, a tablet or a powder of sulphathiazole or a mixture of sulphanilamide and sulphathiazole ($\frac{1}{2}$ grain of each in a tablet) is placed in an extraction socket, there is reason from the greater local concentration to anticipate a favourable issue in the prevention of an infected socket (Krogh, 1948).

The systemic use of sulphonamides has been narrowed down to a choice between sulphathiazole, sulphadiazine, sulphadimidine (synonyms: sulphadimethyl-pyrimidine or sulphamezathine) and sulphamonomethyl-pyrimidine (synonym sulphamerazine). These are usually administered in a loading dose of 2 to 4 grammes, followed by 1 to 2 grammes at four hours or longer up to a maximum of 30 grammes. Sulphadimidine and sulphamerazine rarely cause nausea and give least risk of renal complications from crystallization of their acetyl derivatives which are fairly soluble. Being more slowly excreted, they may be given at six- or eight-hour intervals. In the unpredictable sensitive person, however, there is the possibility of skin sensitivity, aplastic anæmia, or agranulocytosis.

Sulphonamides systemically have achieved remarkably good results as a prophylactic against spread of infection in jaw injuries, alveolar abscess, cellulitis and osteomyelitis before and after operation, but resolution of local infections cannot be expected without surgical eradication of the infected focus—a fact that is sometimes overlooked by medical practitioners.

Penicillin

Five penicillins are now known, differing in their side chains: Pentenyl-penicillin (I or F), benzyl-penicillin (II or G), hydroxybenzyl-penicillin (III or X), amyl-penicillin (dihydro-F) and heptyl-penicillin (IV or K), the last of which is much less effective. The standard is penicillin II or G. In this country, penicillin is used as the sodium or calcium salt but in America the less hygroscopic potassium salt is commonly employed. This is now being made in Britain.

The *mode of action* of penicillin is probably to interfere with amino-acid metabolism by preventing the passage of glutamic acid through the bacterial membrane. It is bacteriostatic, or, in sufficient concentrations, bactericidal, and acts on dividing, but not on resting, organisms. Its activity is not impaired by pus or bacterial debris, but it is inactivated by acids and by the enzyme, penicillinase, formed by *Esch. coli* and *B. subtilis*, and other organisms.

It is effective mainly against Gram-positive organisms, but the individual sensitivity of organisms varies greatly.

Organisms Affected

The majority of indigenous and casual oral organisms are sensitive to penicillin, including *Actinomyces bovis*, *Borrelia* (*Spironema*) *vincentii*, *Fusiformis dentium* (*B. fusiformis*) and *Lactobacillus acidophilus*, although these have a relatively higher and variable resistance. Insensitive to penicillin are the Gram-negative: *Hæmophilus influenzæ*, *Klebsiella pneumoniæ* (Friedländer's B), *Pseudomonas aeruginosa* (*Ps. pyocyanea*), *Aerobacter aerogenes*, and the yeast *Monilia* (*Candida*) *albicans*.

The action of penicillin is not immediate and this presents dental problems for the maintenance of its local activity. MacGregor and Long (1945) reported that the effect of penicillin, whether used locally or systemically by injection, on the oral bacterial flora was at first a rapid fall in the numbers of sensitive organisms, succeeded after about three days by a secondary phase of invasion by insensitive Gram-negative organisms of the Bacterium group, which by producing penicillinase, impaired the efficiency of the penicillin, and thus enabled the former Gram-positive organisms to return (Long, 1947).

Recent American experiments have been directed to discovering the effect of penicillin on the Lactobacillus, but the results obtained, having regard to the wide natural variations in the oral bacterial flora, are certainly inconclusive. A variable reduction in Lactobacilli —as well as in more sensitive organisms—has been demonstrated associated with increases in the numbers of Escherichiæ and Aerobacteriæ, but there is no unequivocal evidence of a striking or even significant reduction of Lactobacilli by penicillin in lozenges, chewing gum or tooth powders, nor acceptable evidence of control of caries by its use (Hill and Kniesner, 1949; Hill, Kniesner and White, 1949; Slanetz and Brown, 1949; cf. Hill, 1948).

Methods of Employment

Calcium penicillin cones or tablets (1,000 to 15,000 units) some of which also contain ½ grain each of sulphathiazole and sulphanilamide, have proved effective in the prophylaxis and treatment of septic sockets; dusting powders of similar composition are valuable locally in osteomyelitis and periostitis after operation. The considerable retarding effect of penicillin on blood coagulation and clot contraction, recorded by Fleming and Fish (1947) must here be recalled. This defect can now be overcome by inserting the penicillin tablet or cone, and spraying or painting the extraction wound with thrombin solution (5 units per ml.) ; the thrombin annuls the penicillin's anticoagulant action without impairing its bacteriostatic powers (Peter and Little, 1948).

Infected root-canals were treated with penicillin initially by irrigation, sealing, or points impregnated with solutions of 5,000 to 20,000 units per ml., but with uncertain results. A meticulous determination by Stewart (1948) of the capacities of root-canals showed volumes in incisors of about 0·01 c.c., for canines and premolars of about 0·02 c.c. and for molars about 0·035 c.c., hence of a 10,000 units penicillin solution per ml. only from 100 to 350 units would be available in the canal; also an aqueous solution of sodium penicillin is absorbed from the canal in twenty-four hours. By the use of suspensions of 600,000 units of calcium penicillin per ml. of arachis oil, a potential root-canal content of 6,000 to 20,000 units can be gained and sterility can usually be attained after one application; the oily suspension remains active for at least a week. Failure may, of course, occur if penicillin-resistant organisms are present (Grossman, 1948; Grossman and Stewart, 1949; cf. Buchbinder and Schwartz, 1948).

Systemic penicillin, when injected as the aqueous solution, *injectio penicillini* (50,000 units per ml.), is excreted rapidly by the renal tubular epithelium; three-hourly injections were first employed; now, with adequate supplies it may be injected in doses of 100,000 to 500,000 units thrice to once daily respectively. Delayed absorption is achieved by the use of *injectio penicillini oleosa* (calcium penicillin with 4·5% white beeswax in arachis oil or ethyl oleate) containing 125,000 units or more per ml.; of this, 300,000 units in twelve, or 600,000 units in twenty-four, hours is desirable. Delayed absorption is also gained from the less soluble procaine-penicillin—a suspension of penicillin (300,000 units) with 0·12 gramme procaine and 2% aluminium stearate in 1 ml. of arachis or sesame oil. This gives an initial blood-serum level of 0·2 units per ml. for one to three hours and levels of 0·06 unit per ml. for forty-eight hours; thus one daily injection of 1 ml. is usually sufficient, and with it skin reactions and local pain are less frequent.

A more recent preparation, penicillin S-R (soluble and repository) contains, suspended in water, 400,000 units per ml., of which 300,000 units are insoluble procaine-penicillin and 100,000 units soluble penicillin. This is stated to give a high blood percentage (4 units per ml.) within thirty minutes, and not less than 0·1 unit per ml. during twenty-four hours.

Oral administration of penicillin is now practicable, but becomes expensive because the dose must be about five to ten times that by intramuscular injection as only about one-third is absorbed. Penicillin is destroyed by the gastric acidity, but, beyond that, is readily absorbed in the small intestine. It is best given in 4 fl. oz. (130 ml.) of a 5 or 10% glucose solution containing as buffers, 1 gramme (15 grains) of sodium bicarbonate or 0·5 gramme (8 grains) sodium citrate per 20,000 units. For adults the dosage would range between 100,000 to 200,000 units three-hourly, hence this mode of administration is generally reserved for children to whom 3,000 units per kg. (or 1,400 units per lb.) body-weight is given.

A systemic penicillin "umbrella" is very desirable, if not essential, before and after multiple extractions of teeth with parodontal or apical infection. It involves the injection of 50,000 to 100,000 units of aqueous penicillin an hour or so before operation to gain a rapid peak, and further similar doses at three and six hours afterwards, with possibly a dose next day; or a single injection of procaine-penicillin (300,000 units) one or two hours before extraction. The gain for the patient is decreased inflammatory œdema and post-operative pain, while the rapid healthy granulation and healing are remarkable; there is also a secure insurance against the development of a bacteriæmia, particularly of a subacute bacterial endocarditis (*cf.* Ostrander, 1948); and, for all cases of cardiac disease, it should be a routine even when healthy teeth are to be extracted.

Systemic penicillin should be given prophylactically before, and continued during, local surgical treatment of jaw fractures, apical abscesses, osteomyelitis, periostitis, cellulitis, acute and chronic pericoronal infections, maxillary sinusitis and gangrenous stomatitis (cancrum oris). Its use in such cases prior to surgical measures, or the topical application of penicillin or sulphathiazole to any infected area, should always be considered because, although it will not usually eradicate the infective focus, it will mitigate the local inflammatory reaction and render surgical extirpation of the infected focus less hazardous. Penicillin should never be used as a substitute for surgical treatment of localized sepsis but it enhances the effectiveness of the protective shield of phagocytes against the spread of the local invasion.

In Vincent's infection, particularly at the acute stage, systemic penicillin will materially assist the efficiency of local treatment (Rankow, 1949).

In actinomycosis, as MacGregor (1945) noted, the response to penicillin varies, as strains differ in susceptibility; more recently, Nichols and Herrell (1948) found that by extending treatment over four weeks, penicillin proved an effective therapeutic agent.

Toxic effects from penicillin are practically absent, except that allergic reactions, usually from sensitization by a previous dosage may produce itching erythematous eruptions, muscular and joint pains with stiffness and even asthmatic attacks. These may call for relief by antihistamine drugs orally, such as anthisan (or neoantergan maleate) 50 to 100 mg.

(¾ to 1½ grains) in tablets; benadryl 25 to 100 mg. (2/5 to 1½ grains) in capsules; or antistin 100 to 200 mg. (1½ to 3 grains) in tablets; and for the asthma, theamin (or theophylline monoethanolamine) 0·1 to 0·18 gramme (1½ to 3 grains) in capsules twice or thrice daily is effective; it is also available with amytal as a sedative for nervous patients. The itching is best controlled by a cooling spirit lotion.

Streptomycin

Streptomycin, an antibacterial agent from *Streptomyces griseus*, forms a crystalline base, which is used as the very soluble hydrochloride, sulphate, or calcium chloride double salt. As a mixture of the latter two would precipitate calcium sulphate, a change from one to the other should be avoided or separated by several weeks' interval. Streptomycin is fairly stable below 15° C. but solutions are best freshly prepared.

Dose: by *intramuscular injection* daily 1 to 2 grammes (15 to 30 grains) or up to 20 mg. (1/3 grain) per lb. body-weight in 10 or 20% solution in sterile water or saline.

Streptomycin is bactericidal against many penicillin-resistant species including *Proteus vulgaris*, *Klebsiella pneumoniæ* (Friedländer's B.), *Escherichia coli* (*B. coli*), *Hæmophilus influenzæ*, *Pseudomonas aeruginosa* (*Ps. pyocyanea*), *Brucella abortus*, *Eberthella typhosa* (*B. typhosus*), *Pasteurella tularensis*, and *Mycobacterium tuberculosis*; but resistant strains are liable to develop during treatment.

Taken orally, little is absorbed, but it has been used with favourable results before colonic operations and for infantile gastro-enteritis.

Given intramuscularly, the maximal blood level occurs within one to three hours, decreasing by renal excretion during the ensuing ten to twelve hours. Two injections of 0·5 gramme (8 grains) daily are now regarded as adequate, except in tuberculous meningitis.

Streptomycin has proved effective in bacteriæmia from *Esch. coli* and *Pseudomonas aeruginosa*; in pulmonary infections from *Klebsiella pneumoniæ*, in bacilluria from *Proteus vulgaris*, *Streptococcus fæcalis*, *Esch. coli*, and *Ps. aeruginosa*; in peritonitis, in tularæmia and in meningitis from *Hæmophilus influenzæ*.

It is the most effective drug for miliary and meningeal tuberculosis, but is often only a palliative. Its action is slow and one or two months' treatment is usually advised; even then, its effect may be only arrestive.

Resistant strains of the sensitive organisms may develop rapidly, especially in urinary infections where brief intensive treatment (3 grammes daily in 4 doses) for two to three days is used. In tuberculous infections, resistant strains do not usually appear before the fifty-third day of treatment, but, when developed, remain permanently. These resistant strains limit the duration of an effective dosage and may prevent its useful repetition, while cases with positive sputum will disseminate resistant strains.

In pulmonary tuberculosis, streptomycin should be reserved for recent and progressive lesions which are unlikely to improve on bed-rest, collapse therapy or thoracic surgery; for acute spreads after collapse therapy or operations; and for rapidly advancing cases for which collapse therapy or operative treatment is inadvisable. Streptomycin may so improve the patient's resistance and condition that collapse therapy or thoracic surgery becomes practicable, especially under its protective influence. Tracheal and bronchial lesions respond well; intestinal and peritoneal cases improve but commonly relapse; and in renal tuberculosis, temporary arrest may be obtained. One case of cure of tuberculosis of the tongue has been recorded (Wolfer *et al.*, 1948). It cannot replace surgery in joint or bone tuberculosis.

Dihydro-streptomycin sulphate (Dose: intramuscularly, 1 to 3 grammes (15 to 45 grains) daily; or intrathecally, 0·05 to 0·1 gramme (¾ to 1½ grains) is equal in therapeutic activity to streptomycin and is less liable to produce toxic effects.

Streptomycin has proved effective in root-canal therapy. Absorbent points impregnated with 1 mg. (1/60 grain) of streptomycin and dried were found to eradicate penicillin-resistant organisms, and to maintain an antiseptic efficiency for two weeks (Bartels and Buchbinder, 1949; Keefer *et al.*, 1946).

An oily suspension is more satisfactory and keeps better than an aqueous solution. Grossmann and Stewart (1949) advise a streptomycin-penicillin suspension containing 500,000 units of each in 1 ml. of oil made with potassium penicillin II and streptomycin calcium chloride (0·5 gramme—not the sulphate which is incompatible with penicillin). Root-canals treated with this and sealed with gutta-percha and externally with zinc cement were found sterile in two-thirds of cases after one treatment and in nearly all cases after two treatments. (*Note*: Zinc cements tend to decompose both penicillin and streptomycin).

Toxic effects from streptomycin are seldom troublesome with 1 gramme dosage daily and have declined with the advent of purer products. Headache, skin flushing, faintness and nausea, relievable by antihistamine drugs may occur. Tinnitus, vertigo and deafness from vestibular dysfunction may be transient or persistent, and form a risk in treating meningitis.

Other Antibiotics

Para-aminosalicylic acid (P.A.S.) or paramisan is used as its sodium salt which forms a soluble crystalline di-hydrate and is available as a sterile 20% solution in 10 ml. ampoules. It is bacteriostatic against *Myco. tuberculosis in vitro*; its action is not impaired by serum, and resistant types do not appear to develop. The sodium salt is given orally in amounts of 12 to 20 grammes (180 to 300 grains) daily in divided doses—commonly 3 grammes (45 grains) at two and a half or three hourly intervals for three or six months. It is absorbed rapidly and one hour after a dose the blood level is about 7 mg. per 100 ml. ; but it falls rapidly to almost nil in three hours as renal excretion is rapid. It is not toxic but is unpleasant to take, and may cause nausea and diarrhœa.

Para-aminosalicylic acid seems likely to be beneficial in conjunction with sanatorium treatment for recent acute exudative types of pulmonary tuberculosis by promoting fibrosis of the lesion; also 10 and 20% solutions applied locally have produced very good results in tuberculosis of the skin and of the tongue; such solutions in 2 ml. doses have also been injected into cavities with benefit. Its therapeutic field cannot be fairly defined at the moment but it is unlikely to displace streptomycin. One important point has emerged recently, namely that para-aminosalicylic acid, given in conjunction with streptomycin, appears to delay or prevent the appearance of streptomycin-resistant strains of the tubercle bacillus. On this line of advance, patients are now undergoing controlled treatment and we must await the results.

Aureomycin or *Duomycin*, obtained from *Streptomyces aureofaciens*, is used as a yellow, crystalline, soluble hydrochloride, and given orally in 0·6 to 3·5 grammes (10 to 50 grains) doses daily in four portions (or 10 to 60 mg. per kg. (1/15 to 2/5 grain per lb.) bodyweight); or intramuscularly, 10 to 20 mg. (1/6 to 1/3 grain) daily in sterile saline. It is bacteriostatic, rather than bactericidal, towards both Gram-positive and Gram-negative organisms, and has a wider range than streptomycin, including the Brucellas, Rickettsias and certain virus diseases, e.g. psittacosis and lymphogranuloma. It has given very favourable results in brucellosis, typhoid, typhus and Rocky Mountain fevers, in urinary infections with *Esch. coli* and in syphilis (Willcox, 1949). Side actions are transitory nausea, vomiting and diarrhœa.

Aureomycin—0·25 gramme (4 grains) orally in capsules every four hours during the day —has produced rapid reduction of temperature, pain and symptoms in a variety of oral infections such as stomatitis, gingivitis, pericoronitis, submaxillary adenitis and chronic diffuse osteomyelitis (Jacobs and Jacobs, 1949). Acute ulcerative and necrosing gingivitis, predominantly from Vincent's infection, is also favourably influenced (Goldman and Bloom, 1949), but these are preliminary reports of which confirmation is desirable. Aureomycin borate in 0·5 to 1% solution is not irritant and may prove useful locally.

Chloromycetin, or *Chloro-amphenicol*, obtained from *Streptomyces venezuelæ*, or prepared synthetically, has been used in doses of 2 to 4 grammes (30 to 60 grains) initially and 0·25 gramme (4 grains) for maintenance at two-hourly intervals for similar purposes to aureomycin but I have no records of its use in oral infections.

Tyrothricin, an antibiotic from *Bacillus brevis* and effective against Gram-positive organisms, is supplied as a 2% solution in alcohol; tyrothricin is insoluble in water but the alcoholic solution, when added to water, forms a colloidal suspension. For clinical use 1 ml. of the alcoholic solution of tyrothricin is diluted with 60 ml. of distilled water; this is not irritant or toxic, and has been widely used as an antiseptic lotion for wounds. In strength of 1 : 5,000 (i.e. 1 ml. of the 2% alcoholic solution added to 100 ml. of water) it has been useful when instilled into the infected maxillary antrum. Recently, lozenges containing 1 mg. of tyrothricin with 5 mg. of benzocaine have been introduced for oral and throat infections.

Obtundents

A review of opinions on the obtundents seems necessary in view of the result of work with radio-phosphorus. The majority of obtundents have hitherto been thought to coagulate the contents of the dentinal tubules and thus to decrease their permeability; but, after treating cavities in dogs' teeth with phenol, phenol followed by alcohol, fluorides, or silver nitrate followed by eugenol, and then with a radio-phosphorus isotope—in solution as disodium hydrogen phosphate (P^{32})—for forty-five hours under an amalgam filling, Amler (1948) found that there was increased permeability of the radio-phosphorus into the tubules. On the other hand, the radio-phosphorus did not penetrate a layer of zinc oxyphosphate cement.

Manley and Hardwick (1948) have pointed out that, as the vital dentinal tubules are dependant on the pulp, devitalizing chemicals applied to desensitize the peripheral endings of the tubules may, by penetration, damage the odontoblast layer and induce a pulp reaction.

They regard silver nitrate as being the least risky because it is precipitated as chloride or phosphate; and zinc chloride and formaldehyde as reasonably safe. Sodium fluoride, 33%, although it acted rapidly in an experimental case, produced gross inflammatory lesions of the pulp. Care has commonly been enjoined in regard to the use of the more caustic and penetrating obtundents; but these results suggest that experimental work on similar lines on the effects of eugenol and thymol in experimental cavities would yield helpful information.

Control of Hæmorrhage

The value of drugs in accelerating clotting has always been difficult to assess and all have had their disappointments with metallic and vegetable astringents, with calcium therapy and with hæmostatic sera. There are now available satisfactory preparations from human blood, and substitutes for these.

Human thrombin is a cream-coloured powder, forming an opalescent solution in normal saline (1 unit clots 1 ml. of a 0·1% fibrinogen solution in fifteen seconds). It is issued in containers holding 50 and 500 units. Solutions of human thrombin from 5 to 30 and 50 units per ml. in saline may be applied or sprayed on bleeding surfaces; but they are more commonly used soaked into fibrin foam, which is then applied to the bleeding point, when clotting takes place immediately. Thrombin may be used to annul the anticoagulant effect of penicillin. Bovine thrombin (200 units per ml.) has also been used locally.

Human fibrinogen is a white powder, soluble in normal saline, but, from this, fibrin deposits slowly; hence solutions are prepared immediately before use. Fibrinogen is used as a 1 or 2% solution, along with thrombin to promote its clotting, in order to cause the adhesion of skin grafts or—although less satisfactorily—of mucous membrane grafts, and to fix nerve sutures; the clot strength depending on the fibrinogen concentration. Fibrinogen is also injected intravenously (10 ml. of a 2% solution) to reduce the clotting time in hæmophilia; the effect lasts for twenty-four to thirty-six hours.

Fibrin foam (*human*) is made by adding thrombin to a foamed 1% solution of fibrinogen and forms a light white spongy material, or, as fibrin film, a thin transparent sheet. Suitable portions are soaked in thrombin solution, and placed on the bleeding point. Blood coagulation occurs at once and the fibrin is left in position to be absorbed.

Fibrin foam with thrombin has been used successfully in controlling hæmorrhage from sockets, but in hæmophiliacs, reliance should not be placed on purely local measures (Henry, 1947). For antiseptic purposes, there may be incorporated with the thrombin solution, penicillin or tyrothricin.

Gelatin sponge or "gelfoam" is a water-insoluble gelatin foam, used in the same way as fibrin foam, with or without thrombin, and it is well tolerated by the tissues (Gwinn *et al.*, 1948). It has also been used soaked in bovine thrombin (200 units per ml.) containing 200,000 units of penicillin and has proved an effective hæmostatic for primary and secondary hæmorrhage in extraction wounds (Silverman, 1949).

Oxidized cellulose or "oxycel" is prepared by nitrogen dioxide oxidation of cellulose into cellulosic acid. It has a pH of 4, and inactivates thrombin and also penicillin, unless it is first immersed in 1% sodium bicarbonate, but this tends to weaken the strength of the cellulose. It is effective without thrombin and is said to form a coagulum of salts of cellulosic acid with hæmoglobin. It is used, after dipping in sulphathiazole powder, as a plug.

Sodium alginate is obtained from the Laminaria seaweed and is a white or yellowish powder which slowly forms a viscous solution in water. When applied in 1% solution to raw tissues, it is precipitated as calcium alginate which acts as a hæmostatic and is later absorbed. Gauze impregnated with the powder may be applied to the bleeding area or a solution of the powder applied on gauze and then sprayed with an isotonic solution (2·5%) of hydrated calcium chloride. Absorbable surgical gauzes and wools are available made from calcium alginate fibres.

More critical clinical experience than is available at present will be necessary to convince me that these substitutes for the blood proteins have a direct hæmostatic action when used without thrombin. They do, however, provide an absorbable skeleton mesh on which clotting is facilitated.

Hyaluronidase

The *mucolytic enzyme, hyaluronidase*, which has recently become available under the name "hyalase", may have dental applications. Hyaluronic acid, a mucopolysaccharide forming viscous solutions, is considered to be the tissue-cement substance. It is polymerized and its viscosity greatly reduced by the enzyme hyaluronidase, which has been called the "spreading factor" for injected fluids. When fluids are injected under its influence, they diffuse rapidly into the surrounding tissues without causing local swelling. The usual dose is 1 mg. (1,000 units) of the powder dissolved in 1 ml. of sterile water, freshly prepared, and it is injected into the tube conducting the fluid for subcutaneous infusion.

Hyaluronidase has been used to increase the area rendered anæsthetic by procaine to almost double. To 50 ml. of a 1% procaine, 0·8 to 1·6 mg. of hyaluronidase was added, along with 0·5 ml. of 1 : 1,000 adrenaline in some cases. Although it increases the area of anæsthesia—more so with adrenaline—it shortens the duration because of quicker absorption. Within five minutes of its injection, without adrenaline, the area which corresponds with the anæsthetized zone becomes erythematous; with adrenaline, the area is blanched. Some tenderness in the area may be felt (Looby and Kirby, 1949).

It has also been suggested that the destruction of interfibrillary cement substance in parodontal disease may be due to hyaluronidase formed by the bacteria in pyorrhœal pockets (Goldsmith, 1949).

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Dr. Alexander MacGregor agreed entirely with Professor Dilling's suggestion for discarding those drugs which had become redundant. Thus, the use of tricresol in pulp canals, still continued, had been shown to be harmful in many cases. Iodoform which had long been discarded in general surgery was still very frequently employed, and there were other and better antiseptics. Iodine was used for painting on to the mucous membrane immediately before local injections though it was known that it took some considerable time to exert any action. The use of sulphonamide powders in sockets and the use of solid sulphonamide or penicillin cones frequently gave rise to trouble for mechanical reasons in hindering the clotting of blood. Professor Dilling mentioned the use of injections of penicillin in Vincent's infection. Heavy doses of at least half a million units had to be given to affect the oral flora. The speaker still preferred local treatment with penicillin pastilles, but stressed the better results obtained with a gelatin base. Professor Dilling had rightly drawn attention to the dangers of the empirical use of penicillin, the abolition of penicillin-sensitive organisms allowing relatively insensitive types to multiply, these organisms liberating penicillinase which destroyed the penicillin and allowed a return of the original infecting organisms. The speaker entirely agreed that the evidence that the presence of the ammonium ion was the best or only factor in inhibiting the Lactobacillus should be treated with reserve as it was known that many other substances would inhibit the growth of this organism. Further evidence was needed in addition that the Lactobacillus had anything to do with the causation of dental caries.

Section of Dermatology

President—W. N. GOLDSMITH, M.D., F.R.C.P.

[*October* 20, 1949]

Familial Benign Chronic Pemphigus (Hailey-Hailey).—R. B. COLES, M.R.C.P. (for SYDNEY THOMSON, M.D.).

Miss C. S., aged 34; occupation, milliner.

History.—Onset of skin trouble on back of neck and thighs five years ago (i.e. at 29 years). At first these patches did not bother her much ; they waxed and waned in extent and severity and occasionally disappeared. Decided worsening occurred in hot weather.

Deterioration in the condition of the groins and neck followed an attack of bronchitis in January 1949 (this was treated with penicillin). Three months later lesions appeared in the armpits and antecubital fossæ. She was admitted to hospital on June 24, 1949.

Condition on admission.—Skin: Lesions were present on the sides of the neck, the axillæ and groins, and the antecubital fossæ. Detailed examination revealed erythematous patches covered with moist scales, and showing marked fissuring. The raw red base of the lesions could be seen in the depth of the fissures. The scaling at the edges suggested fused, flaccid bullæ, but no fluid-containing lesion has been seen in this case. This undermined epithelial border spread peripherally and showed circinate configuration, particularly at the sides of the neck.

Nikolski's sign negative.

General physical examination revealed no abnormality.

Present condition.—Slight residual lesion on left at the back of the neck. Axillæ much improved, lesions paler and much flatter. Antecubital fossæ clear. Groins are still hyperæmic and have improved less than the other regions.

Family history.—The patient is one of a family of nine, five of whom (two sisters and three brothers) are said to have the same condition. Her eldest sister, aged 40, has been examined by us. She had similar lesions in the same sites as this patient and a true bullous fringe at the edge of the lesions in the left axilla.

Treatment has included fractional doses of X-rays to the groins, a course of aureomycin and a small blood transfusion.

Investigations.—W.B.C. 8,500 per c.mm. (neutros. 66%, eosinos. 9%, lymphos. 22%, monos. 3%).

Potassium iodide patch tests negative.

Fungus: None seen on direct examination of several specimens of skin; none cultured.

Biopsy from left antecubital fossa (Dr. C. F. M. Hall).—Section shows moderate acanthosis and a little patchy parakeratosis. There is a well-marked dyskeratosis with acantholysis, the clefts tending to run both horizontally and vertically. The cells around the edges of the clefts show shrinkage and there are very occasional lymphocytes and polymorphs in the acantholytic area. The superficial corium also shows a little infiltration by lymphocytes and polymorphs, mainly focal.

Conclusion.—The appearances are compatible with those described in benign familial dyskeratosis (Hailey-Hailey syndrome).

Comment.—We regard this as a typical case of Hailey and Hailey disease. The history of attacks and remissions, the age at onset and all the clinical and histological features resemble those described in the literature. The apparent high family incidence of the condition is of interest. Here, 8 out of 18 individuals in three generations may be affected. Becker and Obermayer mention 27 cases out of 78 in three generations and this high case incidence in affected families seems to be a common feature, although isolated cases are described. It is also interesting that in this family the males are troubled principally by eruptions on the neck; perhaps this is related to collar-wearing.

Another feature of this case is the worsening which occurs in hot weather. Furthermore, we are told that two of her brothers have had attacks for the first time in this year's hot summer. It seems possible then that heat may be a precipitating factor in some cases of the disease.

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Chronic Benign Familial Pemphigus (Hailey-Hailey).—STEPHEN GOLD, M.R.C.P.

Mr. W. R., aged 69, reported to St. John's Hospital in June 1949 complaining of an irritable rash on the back of the neck, cheeks and chin. He said that it had first started when he was 40, was generally confined to the hairy areas and was entirely dependent on temperature. He was not affected in the winter and the rash would appear after the first hot, sunny day. No treatment had been of any avail and greases tended to make it worse.

He described the initial lesions as blisters, sometimes as large as a pea, which would occur on the friction area at the back of the neck, the penis and scrotum and occasionally on the backs of the fingers and on the dorsal surfaces of the toes. As the blisters developed, itching was intense. Once they had been ruptured after scratching, the irritation was relieved. A clear fluid would exude on rupture of the blisters and a crust would form. The crusts would fall off after some days and no scarring would result.

On examination the only lesions of importance were on the back of the neck. They appeared as superficial, crusted lesions which were grouped in almost herpetic fashion. A few small blisters were also present. There was no Nikolski's sign.

Family history (*see* Fig. 1) reveals that the patient's mother suffered from the same condition involving the back of the neck. Two of his sisters are also affected, with particular involvement of the axillæ and perinea. The patient's daughter suffers from pea-sized blisters on the legs, axillæ and perineum.

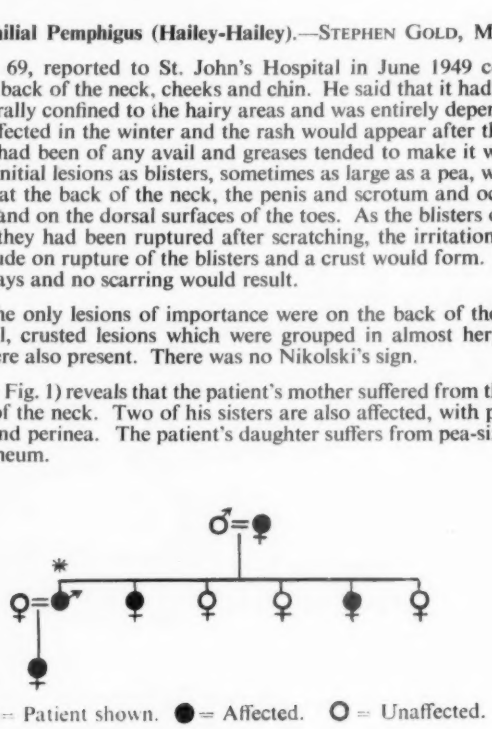


FIG. 1.

Treatment given over varying periods included sulphadiazine by mouth and later vitamin A. Local applications were not well tolerated on the whole. The lesions cleared with the onset of the cooler weather; but before this some developed on the temples for the first time. It seems that more sites are becoming susceptible to the blistering process

[Slides were on view.]

Benign Pemphigus.—R. J. CAIRNS, M.R.C.P. (for G. B. MITCHELL-HEGGS, O.B.E., F.R.C.P.)

Mr. S. K., aged 41, a Pole.

Nine years ago small bullæ occurred over the presternal region and were followed a year later by similar lesions on the sides of the neck. Four years ago the axillæ and groins were affected and two years later the occipital region. There has been no seasonal variation, nor has there been any involvement of mucous membrane. From January to June this year (1949) the skin was almost clear.

Family history.—No history of similar disorders.

On examination.—The scalp is clear. There are brown, pigmented macules on both sides of the neck. At the apex of each axilla the skin is moist and macerated with fine fissuring, and surrounding this area there is brown pigmentation of arciform outline and scattered bullæ up to 1 cm. in diameter. The skin of the groins, scrotum, perianal and internatal regions is slightly vegetative and sodden. The feet show mild interdigital scaling from which fungus has been isolated. Nikolski's sign is negative.

Investigations.—Blood count normal. W.R. and Kahn negative.

Histology (Dr. L. Crome).—"There is hyperkeratosis but no parakeratosis and the stratum granulosum is not well marked. The malpighian layer is thin in places and normal in others ; there is no acanthosis. Many cells in the malpighian layer show hydropic change and, in addition, there are numerous empty spaces in it. These spaces, which were probably filled with fluid, are situated in the stratum spinosum, being separated from the papillary layer by a single layer of basal cells. The papillæ are often elongated and project in a finger-like fashion into the bullæ. The basal cells contain a moderate amount of melanin. There is very little inflammatory change in the corium and the amount and distribution of elastic tissue are within normal limits.

"The above changes resemble those described by Hailey and Hailey in benign pemphigus."

Tzanck test: Smear from the blister contents shows dyskeratotic cells.

Progress.—After three days' sulphapyridine therapy, the lesions became more itchy and new blisters appeared.

Present treatment.—Vit. A 100,000 i.u. daily. Lot. plumbi and glycerin topically.

Familial Benign Pemphigus.—R. J. CAIRNS, M.R.C.P. (for I. MUENDE, M.R.C.P.)

Mrs. K. C., aged 43, housewife.

Twenty years ago a bullous eruption began on the right side of the neck and recurred in attacks lasting six to eight weeks during the summer months only. Seventeen years ago the attacks became more severe, involving both sides of the neck, and a year later blistering and fissuring occurred in the axillæ. The lesions only appeared in hot summers; during cool summers she was completely free. Five years ago blisters and maceration occurred in the groins. Two years ago she was given a course of intramuscular penicillin injections with no effect, since when the eruption has been almost continuous, except during June of this year (1949).

Family history.—One brother has similar lesions in the inguinal region. Her father and paternal grandmother had a similar eruption.

On examination.—The scalp is clear. There are pigmented macules on the side of the neck. The axillæ have central maceration with fissuring, peripheral pigmentation and small bullæ. The inner aspects of the thighs show grouped lichenified papules. The skin of the groins is spongy and fissured. Nikolski's sign is negative. The nails are normal.

Investigations.—Blood-count within normal limits.

Tzanck test: The smear showed dyskeratotic cells.

Histology (Dr. H. Haber).—"The epidermis shows mild hyperkeratosis, patchy parakeratosis and irregular acanthosis. Within the stratum malpighii there are clefts running partly parallel and partly perpendicular to the surface of the epidermis. The clefts have developed into true intra-epidermal bullæ. This change in the epidermis is due to a dyskeratosis of the malpighian cells. They have lost their prickles and have become spherical. Individual and groups of dyskeratotic cells are clearly visible within the bullæ. There is another group of cells scattered within the epidermis which show a granular degeneration of their cytoplasm. The masses appear as purple globules within the cell itself and seem to press the nucleus to the periphery. The nuclei in these cells appear flattened or half-moon-shaped. Cytological scrapings show these cells in a considerable number.

Corps ronds or grains are absent. The upper corium shows a diffuse round-cell infiltration. The elastica appears atrophic in the stratum papillare and subpapillare and looks normal in the rest of the cutis. The appendages show no change.

"Familial benign chronic pemphigus (Hailey-Hailey)."

Comment (Dr. Cairns).—The problem with any new clinical entity such as this is whether it is a relatively fixed variant of some known disease or a disease *sui generis*. Cases have been recorded conforming closely, both clinically and histologically, with those presented to-day. Pels and Goodman (1939), described such a case as "Darier's disease with vesiculation". Hailey and Hailey (1939) introduced the term "familial benign chronic pemphigus", and Ayres and Anderson (1939) reported on five cases under the title "recurrent herpetiform dermatitis repens". The condition was familial in four of their cases. Becker and Obermayer (1940) suggested the term "dyskeratosis bullosa hereditaria".

Although histologically such cases are reminiscent of Darier's disease, I think it more likely that the disorder should be related to epidermolysis bullosa on account of the frequent familial incidence and association with trauma.

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General Discussion on the Four Cases of Benign Pemphigus

Dr. F. F. Hellier: We are fortunate to-day in seeing so many cases of this condition. It cannot be a new disease and I am wondering what diagnosis was given in the past to such cases. I have seen one or two very similar patients who have usually been labelled, rather unhappily, pemphigus vegetans; looking back I feel sure that they have had this condition. The histology is strikingly like what is found in Darier's disease although there is not much clinical resemblance. One point which may have some bearing is that, in patients with Darier's disease, French workers have shown that pathological lesions occur on normal skin following exposure to actinic rays. In the cases under discussion a rather similar feature is that they are mostly worse in hot weather.

Dr. W. J. O'Donovan: We are much indebted to Dr. Cairns for presenting his cases as linked on to an established and recognized group of phenomena and not as examples of a self-existing entity. I have seen this condition previously and because of its association with friction, its unmistakable inheritance and its non-progressive state I have labelled it as a fragilitas dermis. To describe this condition, and others, as a distinct thing discovered at a point in historical time and linked with the name of its first observer is, I think, most respectfully, a rather strong assumption that the disease was missed by the very great clinicians of the past. The addition of names to names in dermatology is burdensome to the newcomer and brings upon us the reproach of physicians who are abandoning this habit in the wide and unitary consideration of cases that now obtains in general medicine.

Dr. Sydney Thomson: I am rather worried about Dr. O'Donovan's objection to the name which has been given to the condition. Even if he calls it "fragilitas dermis", it is still a name attached to it and one which is less distinctive. Certainly when this disease is seen it presents a very definite picture. The changes seen in the axillæ of Dr. Coles' case are most striking, the curious velvety appearance being quite unique and not really coarse enough to be a pyogenic papillomatosis.

The President: Seeing all these cases together, I am inclined to consider this disorder a clinical entity.

Dr. O'Donovan: I do not wish to question Dr. Sydney Thomson's method of approach to dermatology. Our art can be practised by recognitional means by having the exact clinical pictures and by comparing case with case. When Baretta's moulages began to be collected in Paris, French clinical dermatology reached a very high pitch of precision, but I would suggest to our young colleagues that they can practise dermatology to-day by considering more the processes taking place and using a nomenclature that groups together similarities of process; and it was because Dr. Cairns adopted this that I ventured to congratulate him, and I still do, on stressing similarities rather than making a particular point of a new, or almost new, identifiable separate disease.

Dr. F. R. Bettley: I wonder what eventually happens to these cases. I had a patient of this sort in 1938, but afterwards lost sight of him. Quite recently I found that he had got much worse and died in 1941, diagnosed as a case of pemphigus vegetans.

Dr. Gold: The mother of my patient, who suffered from the same condition, died in old age. My patient is 69, and has had the condition for twenty-nine years. It has not become worse during recent years.

Dr. Coles: The mother of our patient shown to-day has had the condition. She is now 64, and is vastly improved. She has had no trouble in recent years except a little during the early summer of this year. One of her sisters, now dead, was affected, but did not die from the condition as far as we know.

Light-Sensitization.—H. W. BARBER, F.R.C.P., and PETER SMITH, M.R.C.P.

Mrs. V. B., aged 43.

At the age of 7 the patient developed eczema of the face and neck following several months' hospital and sanatorium treatment for pulmonary tuberculosis. In the next ten years the rash began to involve the trunk and limbs, especially the light-exposed areas. Since then acute attacks have followed exposure to sunlight and have necessitated her staying indoors much of the time in the summer. There is considerable improvement in the winter months. The irritation is often increased a few days before and during the periods.

General health has been good apart from an attack of pleurisy and bronchitis at the age of 25, for which she was kept in bed six weeks.

Family history.—The father suffered from asthma, and the mother died of tuberculosis at the age of 39. One sister has diabetes, and the brother died of tuberculous meningitis.

Present condition.—In May 1949 the face, ears, anterior part of neck, hands, forearms and shins showed a chronic lichenified erythematous and papular eczema. General physical examination revealed no abnormality with the exception of a liver enlarged to three finger-breadths below the costal margin. Investigations failed to explain this enlargement.

Investigations.—Blood count within normal limits.

Blood urea: 27 mg./100 ml. Liver function tests normal. Urine normal; no porphyrins found. Chest X-ray normal. Mantoux test: Old Tuberculin, 0·1 ml. of 1 : 1,000 gave a strongly positive response with local erythema, induration and spread along the lymphatics, followed by an eczematous reaction on the red area.

Progress and treatment.—In previous years all local applications of light-protective substance have proved valueless, and radiotherapy and œstrogens have been equally disappointing. Investigations in hospital failed to detect any underlying abnormality, except a markedly positive Mantoux reaction in a patient whose light sensitivity followed an attack of pulmonary tuberculosis. In case there may have been some relationship between the development of these two hypersensitivities it was decided to start a desensitizing course of tuberculin. On June 27 the first dose of Old Tuberculin 0·00001 mg. was given intradermally, and the dose was increased each week until 0·0624 mg. was reached on September 25. These doses were tolerated with slight local reaction for the first two months, but more recently there has been a typical tuberculin response appearing twelve hours after the injection as an indurated erythema 3–4 cm. in diameter, and on one occasion, a focal eczematous reaction at all the sites of previous injections.

A tuberculin jelly patch test performed on October 12 was negative.

No other general or local treatment has been given since May, and never has the light sensitivity been less than it was this summer.

Dr. H. W. Barber: When I first saw this patient, I realized that her light-sensitiveness was of what I term the "adult" type, i.e. epidermal sensitiveness with eczematization, severe itching, and secondary lichenification. But in these cases the sensitivity nearly always begins in middle-life, whereas in her case it began in childhood.

Dr. R. Kauntze kindly admitted her for investigation. The adult cases usually show evidence of hepatic insufficiency, but investigations for this were negative, and the only striking features were the family and personal history of tuberculosis and the reaction to the Mantoux intradermal test to tuberculin, the site of which became acutely eczematized. This suggested that her initial infection with tuberculosis in childhood had sensitized the skin to light.

I would not stress too much the therapeutic effect of the intradermal injections of tuberculin as their action may have been non-specific.

Dr. O'Donovan: The tuberculous causation of this condition has been a matter of consideration, of search and research for some decades. I confess I had given up stimulating my assistants to persevere in this for a long time, but when my friend and colleague, Dr. Barber, shows that he pursues this line of investigation with some hope we shall all be stimulated once more to include this, at least for a while, once more in our routine investigation of this type of case.

Ichthyosis Congenita—Early and Late Phases.—C. H. WHITTLE, M.D., and A. LYELL, M.B.

The two patients shown represent two families affected with ichthyosis congenita.

CASE I.—Infant aged 3 months.

In the first family there have been two affected infants both of whom we have examined. Their lesions were identical in kind; in degree the elder was more severe, and survived only

two days. They both showed the characteristic features of the condition—ectropion, eclabium, deformity of the nose and ears, flexion of the digits, and the body covered in a glistening skin, which in both cases had already fissured at the time of birth, though less so in the surviving infant. The name of "collodion fœtus" is derived from this covering. The infant who died was healthy apart from the skin, and, in particular, the post-mortem failed to reveal any endocrine abnormality. The chief histological change in the skin in both cases was hyperkeratosis. The surviving infant's skin proceeded to exfoliate, and after a week the ectropion and other facial deformities had disappeared; in a month the last traces of the "collodion" had gone from the hands and feet. At the age of 3 months the skin remains slightly scaly, but the child is thriving.

CASE II.—The girl, aged 18, represents the second family, in which there were also two affected children. They were "collodion fœtuses" according to their mother's account, which is very circumstantial. This girl now has an ichthyosis of the abdomen and back, involving the groins, and to a lesser extent the axillæ, but sparing the limbs, whose skin is normal.

The details of the family histories are shown below. The affected members are indicated by ♀ ♂



In neither family was there any consanguinity or skin disease.

In conclusion there are two interesting speculations. First, what will happen to the baby? We think that it may recover completely, and are supported in this by the literature. Second, what is the diagnosis of the 18-year-old girl? Has she got ichthyosis vulgaris? Or does the normal skin of her limbs and the mild involvement of the axillæ justify a diagnosis of Brocq's ichthyosiform erythrodermia?

The President: It is extraordinary how rapidly such babies recover, though often incompletely, from their original alarming state.

Chronic Granuloma of the Nose: For Diagnosis.—R. H. MEARA, M.R.C.P. (for W. N. GOLDSMITH, M.D.)

S. P., a Singhalese male, aged 55, who has been resident in this country since 1917.

The patient noticed a small papule on the nose ten years ago. Similar papules appeared nearby forming a lobulated soft mass which enlarged by peripheral extension until it involved most of the surface of the nose and, a few years ago, spread on to the left cheek. About five years ago a pustular eruption appeared on the chin and this has persisted. His general health has been unimpaired.

On examination.—There is a purplish lobulated fleshy mass growing over the nose and extending on to the left cheek (Fig. 1). Sebaceous material can be expressed from this lesion, which is not tender. The mucosal surfaces are not involved. There are also some pustular follicular lesions of the chin.

Investigations.—Wassermann reaction negative.

Smear of tissue from lesion: No acid-fast bacilli or Leishman-Donovan bodies seen in suitably stained specimens.

Culture of tissue from lesion: Bacteriological: *Staphylococcus pyogenes aureus* cultivated. Mycological: No growth after four weeks' culture on beer-wort agar.

Histological examination.—A biopsy was performed on a tumour in the left naso-labial furrow. In the middle of the section is a dense infiltrate, closely bunched up around the upper three-fourths of a hair follicle which is degenerate. Elsewhere there is a less heavy infiltrate, mainly perivascular. The infiltrate is composed predominantly of plasma cells together with proliferative connective tissue elements and capillaries (Fig. 2). The histology points to the lesion being a granuloma.

Histological examination of a lesion of the nose in 1941 showed a similar picture.

The President: The lesions are very sharply defined for rosacea and the regular culture of *Staph. pyogenes aureus* is against rosacea.



FIG. 1.—Facial appearance, September 1949.

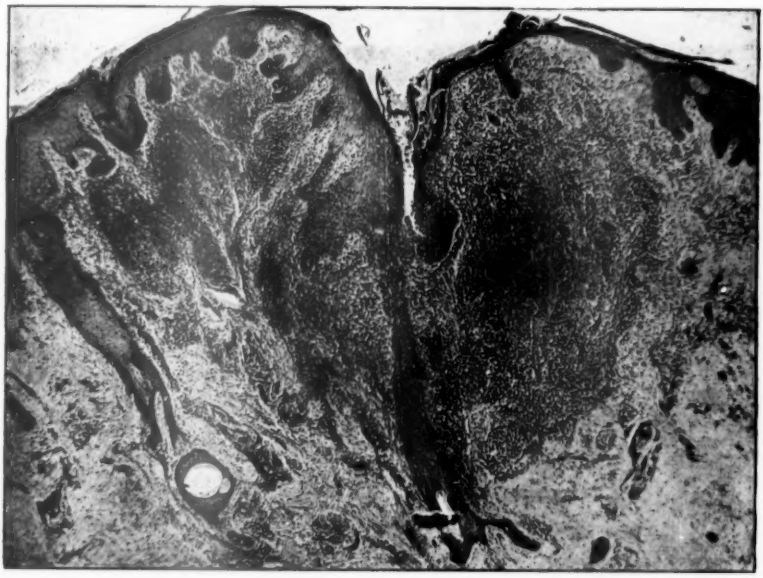


FIG. 2.—Photomicrograph of skin section. (× 50.)

ADDENDUM (23.1.50): Since the above report was written the lesions of the chin have coalesced to form a raised plaque similar in nature to the tumours of the nose. The blood Kahn reaction has become positive but the condition has not responded to anti-luetic treatment. Subsequent cultures of tissue from the nasal lesion have yielded an anaerobic streptococcus and no *Staph. pyogenes aureus* has been isolated in these later cultures. However, a staphylococcal or other cause for this condition is still uncertain. R. H. M.

Localized Pili Torti.—O. L. S. SCOTT, M.B., M.R.C.P.

This patient, a girl of 11, was bitten by an insect on the scalp two years ago. The bite became septic and was incised. Following this, the hair fell out over the lesion, leaving a circular patch about 2–3 inches in diameter. This was bald for three to four months, after which re-growth commenced. The fresh growth of hair was twisted, unlike the rest of the scalp hair. The distortion has diminished lately, and is not so well marked as when first seen some months ago. Microscopically, the hair is twisted in several places through 180 degrees and shows signs of early fracture. [Slide shown.]

Comment.—All cases of pili torti in the literature have the whole scalp involved, sometimes even the eyebrows. The condition seems to be a faulty growth of new hairs, with baldness as an essential preliminary. It usually appears in children aged 1–2 years who have previously been bald, but it has been reported in adults after shedding of the hair. The individual hair is usually short, easily broken and twisted through 180 degrees in several places. It has a strange glint, due to unequal reflexion of light from the twisted hairs.

I have not been able to trace another report of *localized* pili torti. This case fulfils the criteria of pili torti as laid down by Hellier in *Brit. J. Derm.* (1940), **52**, 173.

Dr. H. J. Wallace: It has been suggested that in this case the area might be epilated with X-rays. Such treatment is, however, unlikely to be effective and is not devoid of risk.

The following cases were also shown:

Recurrent Painful Nodules of the Limbs.—Dr. R. M. B. MACKENNA and Dr. E. LIPMAN COHEN.

Congenital Hæmangiectatic Hypertrophy of Ear.—Dr. R. E. CHURCH (for Dr. C. H. WHITTLE).

Phenolphthalein Eruption of Unusual Type.—Dr. DAPHNE ANDERSON.

Pseudoxanthoma Elasticum with Angioid Streaks in the Retinæ (Groenblad-Strandberg Syndrome).—Dr. F. J. JENNER.

Schamberg's Disease.—Dr. E. LIPMAN COHEN.

(These cases may be published later in the *British Journal of Dermatology*.)

Section of Ophthalmology

President—M. L. HINE, M.D., F.R.C.S.

[*October* 13, 1949]

Change and Progress in Ophthalmology

PRESIDENT'S ADDRESS

By M. L. HINE, M.D., F.R.C.S.

IN 1926 our then President, the late Mr. Ernest Clarke, gave a wide review on the progress of Ophthalmology from 1881 to 1926 (*Proc. R. Soc. Med.*, **20**, 70), and this would appear a suitable occasion to continue where he left off, as much has happened in the last twenty-three years. In many cases treatment has improved, new or more perfected operations are being performed, and recently discovered remedies are being used with remarkable results. In addition a lot of spadework has been done on the pathology and biochemistry of the eye, which while, perhaps, not yet yielding its full harvest, may still do so in the future.

OPERATIVE TREATMENT

Detachment of the Retina

The most spectacular advance in surgical treatment has, of course, been that for detachment of the retina, and this dates only from 1929, when Gonin gave, to a rather incredulous Congress at Amsterdam, the results of his patient work over the previous four or five years. After Sir William Lister and Charles Goulden had paid a visit to Lausanne, to study Gonin's methods and results on the spot, the first Gonin type of operation was done at Moorfields in 1930 and I well remember doing my own first one, with very satisfactory result, in February 1931.

During the next year or two ways of obtaining a less localized reaction in the choroid and retina were sought for in this country and abroad and, ultimately, after some considerable trial and error, very weak diathermic currents were found the most suitable and shortly replaced the cautery. This was in 1933, only sixteen years ago. Some favoured the perforating points, others the surface method, while others combined the two. Since that time it can quite fairly be said that, of all unselected cases, some 50% have been successfully treated, according to my observations published in 1944 (*Brit. J. Ophthal.*, **28**, 515) though a considerably higher percentage

cure can be obtained when the material to work on is of better quality and the operator more and more experienced. Arruga, I think very fairly, put it last year at 75%. At any rate this is a very different story from that of the pre-Gonin days, when less than 1% of all detachments were cured by puncture of the sclera down and out, or recovered spontaneously after prolonged rest in bed. When one looks back it seems almost a miracle how, in the course of a year or two after 1929, the teaching on detachments varied from "Holes are hopeless" to "Holes are hopeful".

The success of the operation and the general opinion that most cases of this nature should undergo it have certainly created a problem for the ophthalmic hospitals throughout the country in these days of long waiting lists and nursing shortage. Most cases are of the urgent variety and cannot be kept waiting very long, if at all, before admission. After operation they need a prolonged period of careful nursing for, at any rate, three weeks, occupying much sought after beds. Whereas in 1926 there were 12 scleral punctures done at Moorfields for detached retina, and 8 at the Royal Westminster, in 1947 there were 376 patients operated on by the modern method at the former hospital and 129 at the latter. This problem has still to be solved.

Intracapsular Extraction

A less spectacular advance in operative treatment, less spectacular because it has been more gradual, is the general adoption, in suitable cases, of the intracapsular operation for extraction of cataract. The operation is not a new one and, in 1932, Sinclair, in his Presidential Address to the Annual Congress of the O.S.U.K. at Edinburgh, gave a very full account of its origin. He himself had started operating by this method in 1918, but only as the technique of forceps extraction gradually improved under his guidance and that of Elschnig of Prague and Arnold Knapp in America did it become relatively safe; at the time of his Address practically none were being done in Britain outside Edinburgh. In 1921–2 Foster Moore and Affleck Greeves had used Barraquer's suction method for some months, but the operation was discarded at Moorfields. Apart from this, the first record of an intracapsular extraction to be found in the Moorfields reports is for the year 1932, evidently a response to Sinclair's Address. In 1939 1·7% of all cataract extractions were of this nature at the Royal Westminster. But at the present time all over Britain, as well as in America and on the Continent, this operation is being done in steadily increasing numbers. In 1947 14·25% of all extractions were intracapsular at Moorfields and 12·2% at the Royal Westminster. This percentage seems likely to rise still further as each older and more conservatively minded surgeon is replaced by a younger one. When used with judgment and performed with the necessary skill it must be considered a distinct step forward, not to be overlooked in any progress report.

Squint Operations and Orthoptics

We next come to a very interesting study, which, I believe, must show to everyone the marked influence "Orthoptics", as popularly designated, has had on the treatment of squint. This is a comparison of figures for operations on such cases in 1926 with those for 1947. Orthoptics is by no means a new science, but, prior to 1930, it was not so extensively studied as it now is, nor with such adequate instruments.

It was in that year that the first orthoptic department in a British ophthalmic hospital was opened at the Royal Westminster Ophthalmic and, after that, a new race of "Medical Auxiliaries" rapidly developed. Whatever contrary opinions there may be as to the *extent* of their value in the treatment of squint, there is no doubt whatsoever that orthoptics has come to stay, and that these departments are of great assistance to ophthalmic surgeons; they have influenced their opinion on

operative procedures, including those on the oblique muscles and the superior and inferior recti, and stimulated them to employ the more graded and controllable operations now in use.

Recession of the internal rectus was suggested and practised by Jameson in America in 1922, but did not come into general favour till much later. Williamson-Noble read a paper on "Graded Squint Operations" before the O.S.U.K. in 1929, but the first record I can find in the R.W.O.H. reports is for the year 1931, just after the opening of the Orthoptic Department. In that year seven were done, followed the next year by eleven; since that time the numbers have steadily grown until, as can be seen in Table I, there were 148 such operations in 1947.

Myectomy of the inferior oblique has been done from time to time for over a hundred years, but it is only during the past twenty years that it has been used scientifically. At the present time further improvements in technique are still taking place, and there is a tendency for recession of this muscle to take the place of myectomy in the less marked cases of overaction or contracture.

The first mention of this operation at the Royal Westminster is for the year 1935, when 5 were done, followed in 1936 by 18, with 25 in 1947.

For simplicity in the table I have classed the "resection" operations with the advancements; though technically they may not be identical, in practice they come to the same thing. When considering the figures and comparing what may be called the pre-orthoptic era with the post-orthoptic it must be remembered that squint operations have a very low priority for admittance in these days and that the figures given here for such operations would be much higher if there were no waiting list, on which, at the present time, there are 800 cases for the Moorfields Group.

TABLE I.—OPERATIONS FOR SQUINT

1926	*R.L.O.*	*R.W.O.*
Advancement	20	20
Tenotomy	28	14
Advancement and tenotomy	109	66
Tenotomy with reef stitch	11	—
Various	—	6
Total	168	106
1947		
Advancement (or resection)	31	5
Tenotomy	19	22
Advancement and tenotomy	104	18
Tenotomy (3 snip)	—	7
Advancement and 3 snip		5
Recession	101	148
Advancement and recession	176	161
Myectomy	18	25
Various	30	34
Total	479	425

		R.W.O.H.
First recession	1931	7
First myectomy	1935	5

From the figures given I have myself no doubt that the greater choice of operative technique is a very definite advance on the older and less selective methods, and that the numbers dealt with show the greater care that is being taken in the management of these cases.

Dacryocystorhinostomy

I was rather surprised a few weeks ago when our R.M.O. at the Royal Westminster told me that he had never seen an excision of a lacrimal sac, and only a few days ago his successor told me that the same applied to him. Here was a rather surprising

change in operative treatment, which, on enquiry, I have found to be a definite improvement, though a rather time-consuming one.

In 1926, 96 sacs were excised at Moorfields and 23 at the Royal Westminster. In 1947 the numbers were 44 and 9. But in the latter year 46 dacryocystorhinostomies were done at Moorfields and 22 at the Royal Westminster, while in 1948 the figures for the latter were 3 excisions of sac, and 47 dacryocystorhinostomies.

Once again the operation is not a new one, as Toti first advocated the external route fifty years ago and West the intranasal route in 1920. The operation became the field of the nasal surgeon and not many were done. Some 4 cases a year were sent from the R.W.O.H. to the nose surgeon at Charing Cross between 1926 and 1939. The first record of this operation in the Moorfields reports is in 1932, when the nasal surgeon assisted.

Leighton Davies, in 1934, in a discussion in this Section, certainly stated that he had been using this method for the past twenty years, Pooley in 1925 read a paper describing a rather rough-and-ready operation of this type which he employed in Sheffield, and Traquair in 1932 recorded a number of cases done during the previous few years. But it was not till 1944 that it became increasingly an operation of election amongst ophthalmic surgeons in this country and America, and since that time it has been found to give results which are so marked an improvement on those obtained by the older operation that a majority of surgeons now claim that excision of the sac should never be done except for really old people.

Corneal Grafting

In 1926 corneal grafting had no place in our operative procedures, and all development of this operation in this country dates from the preliminary experimental work of Tudor Thomas from 1930 to 1934, stimulated by the gradual development of a satisfactory technique by Elschnig of Prague between 1923 and 1930.

The first successful graft on a human eye in Britain was done in 1933, and nowadays it is an operation undertaken by many ophthalmic surgeons when a suitable occasion arises. I see that in 1947 5 cases were done at Moorfields and 4 at the Royal Westminster. Long-term results have given rise to some disappointment, but the cases which have permanently benefited are a justification for all the work which has been done, and hold out increasing hope for the future.

Magnet Extraction

I cannot leave this review of changing operative methods without mentioning the changed outlook during the past few years on the extraction of magnetic foreign bodies from the vitreous. It is true that in the 1908 edition of Fuchs' Text Book of Ophthalmology, Duane made the statement that "many prefer even with the Giant Magnet, to make an incision in the sclera as close as possible to the site of the foreign body, previously located by X-rays", but the posterior route never had as many adherents as the anterior. Today the position is largely reversed, partly because so much of the alloy steel now used in the manufacture of tools as well as of weapons of destruction, is only feebly magnetic, and partly because, in these days of diathermic coagulation, surgeons are less chary of making direct approach to the vitreous. It is another sign that ophthalmic surgeons can adapt their methods to the needs of the times.

Non-operative Treatment

Contact Lenses

Passing on to changes in non-operative treatment contact lenses may first be mentioned. The history of their development is concisely given in the recent Vol. IV of Duke-Elder's Text Book of Ophthalmology, and I need only state here that in 1926

it was only very rarely that such a lens was ordered, of the Zeiss type and for conical cornea. The occurrence of large numbers of cases of delayed gas keratitis after the first World War led to the improvement of the Müller type of lens, which was found a more effective form of corneal protection than the Zeiss type, but it was not till 1937 that large-scale facilities for the provision of these lenses became available in this country, first in London, and later in all large centres. As usual, once a facility is provided, fresh uses are found for it and this has certainly proved true of contact lenses. Every new treatment has both its enthusiasts and its detractors, and, in this case, as Cross has recently shown, it is the mean between the two opinions which is proving correct. I learn that some 2,000 patients per annum are supplied with them in Britain, while in America they are being produced in very large numbers.

Transparent Plastic

The adoption of transparent plastic as a suitable substance with which to make some optical appliances is another development of the past twenty years. It was first made by the Imperial Chemical Industries in 1925, but it was not till 1938 that it was first used for making light-weight and unbreakable spectacle lenses. These did not become generally available till 1943, though in 1942 many thousands were sent to Russia. These lenses are as yet too liable to get scratched, but this difficulty is likely soon to be overcome. Quite recently it has been made possible to obtain bifocal lenses, with certain limitations, of this type.

This material has also been more recently adopted for the manufacture of contact lenses and artificial eyes.

Operative Aids

Certain operative aids, now almost routine, were not used in 1926, save very occasionally and individually.

Retrobulbar injections of novocain began to be popularized in 1930, though they had been regularly used by Elschnig a few years before that date, for his intracapsular extractions.

Akinesia of the orbicularis was being practised by Sinclair in 1930, having originally been suggested by Van Lint as long ago as 1914, but it did not come into routine use till approximately 1935–36.

As previously mentioned, diathermy was only adapted for use in ophthalmic operations in 1933, originally for detached retina. Since that time many other uses have been found for it, as Weve showed in his Bowman Lecture in 1939, and the modern surgeon would be very handicapped without it.

We must not forget also that radon seeds for the treatment of intra-ocular neoplasms were first used by Foster Moore in 1929, and, soon after, fractional doses of X-rays were introduced for the same purpose by Martin and Rees in America.

Therapeutic Measures

As regards the newer drugs, Sulphonamides, Penicillin, E.3 and D.F.P., their introduction is so recent that I need only mention them briefly to complete this review.

The German sulphonamide compound, Prontosil, made its appearance in 1935, but only on very rare and individual occasions was it used in this country for streptococcal infections of the eye. It was not till sulphapyridine was manufactured and tested in 1938 that large-scale clinical trials in cases of streptococcal and gonococcal infections of the eye gradually took place. The less toxic sulphathiazole, sulphadiazine and sulphamezathine came one by one a little later, the last in 1942.

In that year, at a discussion at the Annual Congress of the O.S.U.K. on the uses of these sulpha drugs in ophthalmic practice, it was shown that the treatment of ophthalmia neonatorum had already been revolutionized, and that they were of great benefit in streptococcal and pneumococcal infections of the conjunctiva and lacrimal sac. Their value was still being assessed and discussed when penicillin arrived on the scene. The latter was first tried in ophthalmological practice, on a small scale, at the instigation of Professor Florey, at the Oxford Eye Hospital in 1941, but until 1945 supplies were very small and almost all went to the Services. Though not the cure-all popular belief would have it to be, partly because of the difficulties of getting effective concentration in the eyeball, and partly because all organisms are not penicillin sensitive, there is of course no doubt about the great value of penicillin in ophthalmological practice, or that both it and the sulpha drugs have given us an entirely altered outlook on the result of numerous infections of the eye. Ophthalmia neonatorum is only one example. As a more penicillin- or sulphonamide-resistant race of organisms develops we are likely to hear more in the future of other antibiotics, perhaps aureomycin, and one day we may be able to deal successfully with the various virus infections including herpes simplex.

Like penicillin and, to a very large extent, the sulpha drugs, the other two recent additions to our therapeutic equipment, E.3, and D.F.P. are due to British initiative. E.3, the non-irritating synthetic mydriatic, is a product of wartime research, stimulated by the shortage of atropine in 1942–43. Clinical trial was undertaken at Oxford in 1943, and soon after at Moorfields, but it did not become generally available till 1944. It is a definite addition to our therapy, especially in those cases which are, or become, allergic to all mydriatics.

D.F.P., the newest powerful miotic, able to quickly overcome the effects of atropine, is, still more, a wartime development in that it is a diluted product of one of the gases tried out for gas warfare, and, fortunately, never used for that purpose. The effect of this gas in contracting the pupil was noticed first in experimental animals, and this started further experimentation with very dilute solutions, leading to clinical trials which gave promising results, and, in 1946, a further addition to our therapeutic resources.

Brucellosis and Toxoplasmosis

Before I end, I must make brief mention of the research on brucellosis and toxoplasmosis, which has been going on during the past few years on the Continent and in America, work in which ophthalmologists have taken their full share, and I must not omit the clarification of the vascular changes in diabetes by Ballantyne and Lowenstein, work which has stimulated our medical colleagues and pathologists to further investigations.

Though much of what I have brought forward has been illustrated from local sources, I should like to say here that I am certainly not claiming these various advances for British Ophthalmology alone, but for Ophthalmology as a whole; it is international, and in some cases we follow where others lead, while in others it is certainly vice versa.

I know that I have by no means exhausted the subject, and feel that many useful additions could be made; but I think that I have said enough to show that real and steady progress is taking place in Ophthalmology through the adoption of new methods and a gradual improvement of older ones. I hope that this review will stimulate us to further efforts, so that progress may continue. I also hope that more and more mass records as to the results of various treatments and more long-term reviews will steadily become available. These will then be the basis on which some successor of mine in this office will be able, in due season, to give a still more comparative and accurate record of progress during the next period.

Section of Otology

President—GAVIN YOUNG, M.C., M.B., F.R.F.P.S.Glas.

[*November* 4, 1949]

Aural Cholesteatoma—or Cholesteatosis. A Review

PRESIDENT'S ADDRESS

By GAVIN YOUNG, M.C., M.B., F.R.F.P.S.Glas.

IN the writings on this subject, cholesteatoma is referred to, usually, as being either primary or secondary. Pathologists and neurosurgeons have described the former type as the "pearl tumour", or nowadays as an epidermoid. It is met in the bones of the skull, most commonly in the temporal bone, and also, though very rarely, in the substance of the brain.

Jefferson (1938) has published a series of 6 cases of slowly developing unilateral facial paralysis accompanied by some deafness and shown at operation to be due to epidermoid growths. The first case was that of a typical epidermoid, though there was a history of otorrhœa at times in the past. At operation, a large epidermoid was removed which filled almost the whole petrous. The feature of interest and importance in the case was that the mastoid process was normally cellular. In 3 of the cases there was no history of otorrhœa. The other 3 had exhibited suppurative otitis media at one time, but the ears were dry and uninfected at the time of operation. Primary cholesteatoma has been described from time to time by otologists also, but I personally have never encountered a real primary cholesteatoma, or epidermoid, in the mastoid process in the course of some thousands of mastoid operations. I believe with many others that the time has come for a change of nomenclature.

The Greek suffix—*ωμα*, suggests "swelling", and its use has been associated traditionally, in medical terminology, with tumour. There are exceptions, glaucoma and trachoma, for instance, in which the original sense of the suffix has been preserved. The hypothesis of tumour-formation had, of course, something to support it. "Tumour" was the description most apposite to the early otologist when he encountered this foreign, soft mass which had made for itself a bed in densely hard bone. Not merely did the mass resemble a tumour growing at the expense of the surrounding tissues, no matter how dense, but also it had the appearance of local malignancy because of recurrence, in some cases, even after thorough exenteration.

The modern view, however, is that cholesteatoma is not a tumour, and I suggest that the suffix—*ωσις*, meaning "containing" or "full of", may give us a term more suitably descriptive, and more in accordance with recent theories of the pathogenesis of the condition. I propose, then, to speak of "Cholesteatosis".

In my experience, cases of very extensive cholesteatosis are not so common now as they were thirty years ago. The most extensive case I have ever seen occurred in 1914. This was a massive affair which had eroded into the middle fossa and had lifted the brain from the floor of the middle fossa over a wide area. There had been an extradural abscess, lateral sinus thrombosis and a cerebellar abscess—from all of which the patient recovered, after a stormy time, under Kerr Love's patient care. I think that the lessening incidence of this type of case may be due to earlier recognition of the condition, and a disposition, generally, towards earlier operation. There are also many more adequately trained otologists to attend to the work.

Signs and Symptoms

There is usually a history of otorrhœa, either persistent or intermittent, and this is always characteristically malodorous. Since the attic is always the site of the disease from the beginning, the hearing acuity is usually defective, sometimes markedly so. Headache is a fairly common complaint, especially where the discharge is intermittent. If syringing be employed to remove débris the surface of the returned lotion commonly presents an oily appearance, caused by the presence of a fine layer of squames, floating on the surface. Its appearance resembles that of the lotion returned in an antral proof-puncture where a mucocele or retention cyst has been punctured, and disorganized débris and squames are washed out of the antral cavity. Chronicity of disease may be accompanied by extensive damage to the drumhead, to the membrana tensa as well as to Shrapnell's membrane, with protrusion of cholesteatosis from the region of the attic. Members who have attempted to remove the débris of cholesteatosis through the meatus will recollect how tightly the débris is packed and how difficult it may be to remove. I shall allude to this circumstance later. Other signs and symptoms, such as vertigo, elevation of temperature, evidence of increased intracranial pressure, or of a generalized systemic infection, will depend upon the extent and the direction of erosion.

In these cases, the massive type in which the resemblance to a cyst or tumour gave rise to the name cholesteatoma, the pathological entity is a smooth-walled silvery cyst, lying in a bony cavity and easily detached from its bed. The cyst wall consists of concentric layers of epithelium, the parietal surface actively growing and shedding squames, so that the wall is a series of successive layers. Growth of the cyst is probably fairly constant, and takes place *pari passu* with the increase in the contents of the cyst. These are squames, mycelia, cholesterin crystals whose presence is due to the breaking down of the epithelial elements, and the products generally of suppuration.

There has been speculation on the exact procedure of the growth of the cyst. In my view growth progresses at the expense of the surrounding bone by simple pressure erosion, a common thing in pathology. The aortic aneurysm may erode the anterior aspect of the vertebral bodies. One sees repeatedly, invading the antrum, the maxillary cyst, either periodontal or dentigerous, which has grown at the expense of the floor and the anterior wall of the antrum to such an extent as to produce the state of egg-shell crackling. There is an aphorism in pathology that intermittent pressure may cause hypertrophic reaction of the opposing tissues, constant pressure causing atrophy.

I have indicated that the contents of the sac may be firmly held. The principal single factor in promoting growth may well be the introduction of moisture. As Day (1934) has said, cholesteatoma is markedly hygroscopic, and moisture will cause the mass to swell and to exert pressure on the surrounding tissues, even on dense bone. It is likely that the process is one of local anæmia, with atrophy, of the surrounding bone. The presence of moisture, warmth and dead tissue affords a favourable medium for bacterial growth. Day believed that the most important factor in the development and growth of cholesteatoma is the presence of moisture. Whether the moisture is due to suppuration, is a transudate or an exudate or even water, the effect is the same. The surface epithelium of the body does not tolerate well the continued presence of moisture, which causes irritation and degeneration of epithelium.

Under this motive force of growth, cholesteatosis may be regarded as locally malignant, as running wild, and indeed any of the important structures related to the tympanic and mastoid regions may be eroded and destroyed. The condition is not commonly sterile, unless the attic perforation has closed, or, probably very rarely, has never existed. The infection is likely to be of a low-grade type, setting up a degree of local protection, a sort of local immunity. This may be broken down by the introduction of a fresh infection, or by some factor which has caused lowering of local or general resistance, either "chill" or trauma, when a flare-up, with more copious pus formation, under pressure, will transform the condition clinically into an affair of emergency.

In the literature there are many references to the ravages caused by cholesteatosis, and it is this fact, and the necessity of the earliest possible recognition of the condition, which have impelled me to choose this subject for my Address. A spectacular type of case is that in which the radical mastoid operation has been performed by the process of disease. There are those cases, also, in which the widening of the aditus by the cholesteatosis has not quite attained the complete erosion of the bridge. These two types of case are not at all uncommon. Of the considerable number that I have seen, the best result in my recollection was the case of the wife, aged 40, of a colleague, who presented a perfectly healed radical mastoid cavity, never having undergone operation, but having suffered from otorrhœa in childhood. Another point of interest in this connexion was that a son of this patient underwent the mastoid operation at the age of 4, for cholesteatoma, the ear having discharged from infancy. In the case of the mother, the aditus and meatal drainage were widely patent, which doubtless accounted for the fact that the ear was dry, and that cholesteatosis had ceased to form. Others that have been seen in the past have continued to desquamate, with fœtor, and to form the silvery lining membrane. In such cases, the facial ridge has not been lowered sufficiently by the disease to provide easy, unimpeded drainage, with subsequent natural healing.

In contradistinction to Jefferson's cases of epidermoids, Lundgren (1948) reports 4 cases of apex (petrous) cholesteatosis causing progressive facial paralysis, secondarily to mastoid cholesteatosis. In each of these cases there was ample evidence, in middle ear and mastoid, of the presence of cholesteatosis. Indeed the radical operation had been performed in 2 of the cases. Also in the recent literature, Nilsson (1948) reports a case of attic cholesteatosis, following a longitudinal fracture of the petrous. The case is not without interest, being that of a man who suffered a severe skull injury, with bleeding from the ear, and slight facial paralysis, left side. The immediate evidence of damage cleared up save for a slight hearing defect. There was neither discharge from, nor pain in, the affected ear until eleven years later when he developed an epitympanitis with foul-smelling discharge for which he underwent the radical operation. There was cholesteatosis in the attic, but the mastoid process was normally cellular and showed no disease. The normal pneumatization, as I shall remind you later, was unusual.

Pathogenesis

In the past twenty years there have been published by British otologists two very important papers on this subject—by Dan McKenzie in 1931 and Tumarkin in 1938. McKenzie challenged the hypothesis of immigration and Tumarkin dealt it the death-blow.

McKenzie's paper (1931) was read in this Section, a patient marshalling of all the facts and hypotheses known to him on the subject, written in his characteristic and delightful style. He denied the origin of cholesteatosis in the growth into the middle ear of meatal epidermis. He believed that cholesteatosis had a tympanic origin, and after a full discussion he came down on the side of an epidermoid origin. It is suggestive, however, that he had doubts on the subject when he interpolated the passage on " An Objection to the Epidermoid Theory", on the ground that intracranial epidermoids are among the rarest of tumours, whereas aural cholesteatosis is quite common.

It is of more than passing interest to record, as Tumarkin has done, that the President of the Section, A. R. Tweedie (1931) said in the discussion, that he had never been able to accept the theory that cholesteatoma had an embryonic origin, or that it was due to an invasion of the skin of the outer meatus. It was his opinion that the process was dependent upon some past sepsis, often not demonstrable, and that the irritant effect of this on the lining of the antral cavity and mastoid cells, led to an accumulation of an abnormal desquamation. These factors would be sufficient to account for such formations if associated with the one other factor required, a "bottle-neck" cavity. Lowndes Yates also pointed out that the desquamation of the mucous membrane of the middle ear, in cases of inflammation of the middle ear not associated with cholesteatoma, was well recognized, occurring in streptococcal infections more commonly than in staphylococcal infections. He made the point that it did not require a high flight of imagination to postulate desquamation in sheets from infected mucosa, particularly if the infection were caused by streptococci.

In 1938 Tumarkin, gathering together the known evidence, emphasized in his downright way the two major points of importance in the unravelling of the pathological skein. The first referred to the tympanic mucosa, and the second to the defective pneumatization characteristic of cholesteatosis.

Tumarkin pointed out that the middle-ear mucosa was not the same throughout this cavity. The tympanic mucosa was said to be covered by ciliated epithelium, the epitympanic or attic was covered by squamous. The process of enclosed desquamation from the attic pavement epithelium being a strong possibility under certain conditions, it became

unnecessary to postulate a source of desquamation outwith the middle ear. Epithelial ingrowth from the meatus, through a defect in the drumhead, was not required to produce cholesteatosis. In addition, since the initial perforation was always in the membrana flaccida, this might be held to confirm the fact that it is always the pavement epithelium in the epitympanum which desquamates.

The other point of ætiological importance lies in the pneumatization of the mastoid process. It has long been recognized that the mastoid process in the great majority of cases of cholesteatosis shows defective pneumatization. Tumarkin quotes Wittmaack in saying "For many years we have not seen cholesteatoma in a well-pneumatized bone. Even if we do not find a completely compact bone, still there is a very marked reduction of air-cells." Day states, also in support of Wittmaack, that in most cases of cholesteatoma there has been a lack of pneumatization in the mastoid. He says also that the occurrence of cholesteatoma is largely dependent on the altered mucosa of the middle ear, and that a sclerotic mastoid is the result of maldevelopment, not of cholesteatoma. Nilsson (1948) gives the following figures of normal pneumatization in cases of cholesteatoma—Gaben (1936) in 327 cases of cholesteatoma 0·3%, Steurer (1937) in 400 cases, 0·25%, Wustman (1942) in 448 cases, 0·2%. The figures are strikingly similar at 0·2% to 0·3%.

It may be assumed then, that faulty pneumatization is at least associated with, if not directly causal of, cholesteatosis. J. P. Stewart (1928) in a paper on the "Histopathology of Mastoiditis", has contributed much that is of interest in the development of the mastoid, and I take the liberty of quoting him extensively. According to Stewart, the mastoid takes shape only from the start of the second year onwards. Its development may be divided into three periods. The first is the development of the lumen of the recessus and antrum, which takes place in the first year of life. The second period is the development of the pneumatic cells, which normally takes place during the second or third years of life, at least up to the end of the fourth year. If, after the fifth year, the mastoid process is incompletely pneumatized, disturbance of the process has occurred.

The process of pneumatization is as follows: The ingrowing epithelial sac presses upwards, opening up the antral region, the pressure of the growing processes setting up a collateral œdema whereby the parenchymatous element of the bone marrow atrophies, leaving only its framework of endosteal tissue. This becomes myxomatous and is later transformed into loose fibrous tissue which then becomes pressed into a very fine layer on the osseous trabeculæ. It is surmounted by a single layer of flattened epithelium. Simultaneously, widening of the bony walls of the pneumatic cell takes place either by osteoclasts or by perforating vessels. The third period of the development is the further distribution of the pneumatic cells in later life. There are comparatively few completely pneumatized mastoid processes—Ruttin gives about 25% as his figure, and all types may be met with between the completely cellular and the densely sclerotic. Arthur Cheatle states that 15% of mastoid processes are of the acellular type, and 2% of the densely sclerotic type.

Arrested Pneumatization

The normal pneumatization of the mastoid process may be interfered with at any stage of its development by the pressure and effects of local inflammation. Wittmaack has said that in the presence of disease, new connective tissue is formed beneath the epithelial layer of the advancing sac. Consequently, adhesions are formed and growth of new bone takes place, encapsulating the antrum from the spongy mastoid, and so by a mechanical process further pneumatization is prevented. The adhesions form loculi in which the inflammatory processes may continue though in a quiescent form. Staphylococcal infection seems to favour the chronicity and the slow course of the condition.

Stewart states that air plays a very important part in the absorption of exudate from the middle ear, and the exclusion or absorption of air renders the individual more liable to local disease. This is well seen in children where the air content of the middle-ear cleft is very small, and in the incompletely pneumatized mastoid where air may be either excluded or more quickly resorbed. Where blockage of the eustachian tube occurs œdema *ex vacuo* results. The muco-endosteum which normally is pressed flat against the bony wall of the cell, or of the attic, expands to many times its original thickness. The endosteum is spread out into a loose network, according to whether it has been healthy hitherto, or has been the seat of prior infection. Owing to the decreased tension of the supporting tissues, the vessels dilate and extravasation of plasma occurs. When the supporting tissue of the blood vessels consists of well-formed fibrous tissue, the œdema will not be so intense, as the tension will be better maintained. The patency of the eustachian tube has therefore a bearing on the course of local inflammatory disease, in ventilating the cavities of the middle-ear cleft, and in furthering the resorption of serum.

The presence of inflammation, then, or of hæmorrhage, in the middle ear during the first two years of life may prevent pneumatization, and the same pathological process of sepsis may form an adhesive process narrowing the lower inlet of the epitympanic space. This condition may remain completely quiescent for a long period until a local pathological state causes shutting off of the attic. This, in the characteristic state, may be only a very mild catarrhal condition which sets up only minor local danger. The infective agent may be of a type of low virulence, and desquamation of the attic mucosa starts within an intact membrana flaccida. This is shown clinically by dulness of hearing, quite commonly without pain, later by reddening and fullness of Shrapnell's membrane. This may continue for weeks before perforation of this membrane takes place with, usually, very slight discharge which may indeed be shown only as a crust on the drumhead with, however, a purulent underside, observable only on removal. The discharge early becomes malodorous. In time, the perforation becomes definite, there may be a vegetation at the edge of the defect, and the discharge contains squames.

One may envisage the type of case, however, in which the growth of cholesteatosis is so gradual that the membrana flaccida may not be opened, but in which the cholesteatosis may continue to grow and to attain considerable size before becoming a clinical entity. Recently, Riccibona (1948) has reported a case, which he describes as congenital cholesteatoma. A woman of 70 was admitted to hospital unconscious and died. Facial paralysis of old standing was present. She had been unconscious for seven days prior to admission. At autopsy, meningitis was found with a large cholesteatoma between the dura mater and floor of the middle fossa. The membrana tympani was said to be intact and the claim has been made that the cholesteatoma was congenital. It is possible that the growth in this case may have started as indicated above, but of course in the absence of clinical data this must remain an unsatisfied hypothesis.

The middle-ear cleft in infancy appears to be particularly prone to pathological change. The more horizontal slant and the relatively wide calibre of the eustachian tube in the infant tend to place it in greater danger by the canalizing of infection, vomitus, and even hæmorrhage into the middle-ear cleft. The early presence of adenoids must be a very important cause of sepsis in the small cavity of the infant nasopharynx. The presence of adenoids in the first few months of life as a clinical fact is not uncommon. In addition, the association of suppurative otitis media and infantile enteritis is too well known to require more than a mere mention.

It may not be out of place to consider here whether the shape of skull associated with the so-called adenoid facies may not be an important causal factor in nasopharyngeal sepsis leading later to cholesteatosis.

Members will recall the arresting quotation from Hippocrates which used to appear in StClair Thomson's earlier editions—"Those who suffer from headaches and running ears, have high-arched palates and irregular teeth." It is not necessary here to probe far into this question. We do accept, however, that in the adenoid facies, or more properly, the facies of nasal obstruction, there is a very marked tendency to the growth of post-nasal adenoids and sepsis which may later be associated with suppurative sinusitis and sometimes with bronchiectasis. It is many years since one noted the very high incidence of exaggerated adenoid facies among those who suffered from intracranial complication of suppurative ear disease. Naturally a high percentage of these were secondary to cholesteatosis. In these thirty years of the practice of otology I have seen very many instances in which there were several cases of cholesteatosis in two or three generations of one family. The adenoid facies was familial in these cases.

Within the past six months, I have dealt with a case of cholesteatosis from almost the earliest possible clinical existence.

A. C., a nurse aged 23, became suddenly hard of hearing in her left ear in February 1949. There was no previous history of ear trouble save earache in childhood. The patient was in hospital at a distance from her home, and as a result she was in the hands of three different otologists of standing. The condition was thought to be due to a recent acute catarrhal otitis—though there was no history of pain. Reddening of the membrana flaccida became apparent with, later, a minute defect in this part of the drumhead and occasional leakage. The hearing deteriorated further. The patient felt no upset save her hearing defect. The discharge increased, the perforation became more apparent as such, and a small granulation presented. At length there was complaint of pain, five months after the onset of the first complaint. The mastoids were X-rayed, and the right or healthy ear was found to be normally pneumatized, the left being acellular.

In August operation was carried out. As I like plenty of elbow room in operating upon the mastoid the conservative mastoid operation was done, our more convenient name for transmastoid atticotomy. A careful dissection of the upper half of the mastoid and removal of outer wall of aditus and attic showed a small cholesteatosis filling the attic and aditus and extending into the antrum, pushing a

small granulation ahead of it. The long process of the incus was diseased, and the incus was lying partly mobile. The head of the malleus was removed along with the cholesteatosis. The result has been satisfactory, the ear being now dry.

Early recognition of this condition is essential. In my experience, palliative treatment is of value mainly where the hearing remains good, as it does for a time in a limited number of cases. Most cases require operative interference to ensure the drainage and aeration necessary to successful healing.

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Mr. F. McGuckin said that microscopically there seemed no distinction in kind between the preponderantly granulating otitic lesion and that which chiefly exhibited a desquamating keratinizing change. All grades could be found, and the same middle-ear cleft might include both extremes in different parts. It was difficult to explain the solid, clean, dry cholesteatomas varying from the tiny sterile "anterior attic bomb" to a massive involvement of cells and cavities throughout the cleft and even through the tip. He did not understand these lesions ætiologically, and was not fully satisfied that they were wholly infective in origin. Moreover, he remained mystified as to the precise mechanism by which these masses caused such clean, smooth bony erosion—if in fact they were the eroding agent.

He considered that cholesteatoma could be found in cellular bones, sometimes highly cellular, and that in rare cases each cell might be found to contain its own separate cell mass, the pathology extending occasionally as far as the internal auditory meatus. With respect, therefore, he differed from the President's statement that cholesteatoma was found in a bed of hard bone. This was the common but not the invariable finding.

Mr. E. Watson-Williams wondered whether "cholesteatosis" was a happy word. Was the reference to a process or to a mass? They had been accustomed to giving the name "cholesteatoma" to a lump of material and "cholesteatomatosis" to the process of its formation. He felt that the use of the word "cholesteatosis" was likely to present difficulty to many people. "Osis" = process: but now a word ending in "osis" was being used not for a process but for a visible mass.

As to the actual condition, he thought that whatever one's views, one had to take into account, as the President had emphasized, the common association between the acellular mastoid and the cholesteatoma. His own experience was that cholesteatoma was not encountered, or was very rarely encountered in a mastoid, save in cases in which the cells had not developed. His view had been for many years that the acellular mastoid was due to the early arrest of pneumatization and not to sclerosis causing obliteration of the cells which had in the past come into existence. He found it impossible to believe that a pneumatized mastoid could become sclerotic.

But his experience differed from that of the President in respect to the position of the perforation. He thought that the President's point was that the perforation in the case with a cholesteatoma was in the membrana flaccida. In many cases the perforation was in the membrana tensa; but there was a small group in which the space of Prussak became involved and a cholesteatoma emerged there, perhaps destroying the outer wall of the attic and the head of the malleus without, as a rule, affecting the hearing, and quite often without involvement of other parts of the middle-ear tract—a rare and isolated state of affairs. His own view of the cause was that it was always inflammatory. He could not envisage a congenital cholesteatoma. It was so constantly associated with inflammation that he thought that in those cases which were said to have arisen *de novo* without inflammation there must be an inadequate history.

Mr. D. A. Barley said that on this question whether cholesteatoma could occur in an extensively pneumatized mastoid he would like to describe a case. This was of a boy aged 3, who in March 1948 had a history of one week's discharge from the left ear. Its onset was insidious and there was no apparent pain or deafness. Examination showed a posterior marginal perforation of the left drum, offensive discharge and infected tonsils and adenoids, which were removed a few weeks later. Radiological examination showed both temporal bones to be extensively pneumatized. Cells on the left side were uniformly clouded, indicative of infection. Conservative treatment failed to arrest the discharge.

Six months after the disease was first noticed the left mastoid process was explored and an extensive cholesteatomatous deposit found within the left temporal bone. This extended from the tip of the mastoid well into the root of the zygoma. All three semicircular canals, the dura mater and the canal of the facial nerve together with the lateral sinus were exposed. The interesting thing was that the pneumatization patterns of both temporal bones were identical. As the right drum showed a small area with thickening just behind the short process of the malleus it was thought justifiable to explore the right mastoid process in order to exclude the presence of any primary cholesteatomatous deposit. This was done but no cholesteatoma was found in the normally pneumatized right temporal bone. It would be interesting to see, in view of the abnormality of the right drum, whether cholesteatoma would form within what was known to be a normally pneumatized mastoid process. Diamant had published a paper in which it was suggested that marginal perforations might result from primary cholesteatomatous deposits. It seemed incredible that in a child of 3 this cholesteatomatous deposit could result from a marginal perforation with so short a history.

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Mr. Donald Watson said that some years ago, shortly after Dan McKenzie's paper, he saw a child of 7 with a cleft palate and harelip, who was very ill with a right-sided acute mastoiditis and meningitis. In her convalescence she had symptoms of brain abscess, but fortunately this was cerebral œdema and she recovered without intervention. At operation a cholesteatoma was found in the right mastoid. As she had been so ill the parents insisted that the child should come and see him (the speaker) regularly. About eighteen months after the first operation she complained of deafness in her left ear, and making a further examination he found a tiny scab in the region of the attic. He picked it off and it had the appearance which the President had described. Later he had to do a modified radical operation on the left ear where a cholesteatoma was found also. The child had never had earache and there was no history of otitis media. These were undoubtedly primary or "congenital" cholesteatomata on both sides in a child with a cleft palate and harelip.

Dr. Hugo Frey said that he had seen a primary cholesteatoma of the middle ear. Primary cholesteatomata, well known to the pathologist, were found in various bones of the skull—temporal, frontal, occipital—and were considered to be due to primary displacement or disarrangement of the epithelial germs. Then there were cholesteatomata which were secondary to chronic middle-ear suppuration. In addition there was another class, the primary cholesteatoma in close association with the tympanic cavity, and yet having no actual connexion with the cavity itself. He had seen such a case in a patient 50 years of age. The operation which he undertook revealed a cholesteatoma, half the size of his fist, occupying a large part of the posterior fossa. The tumour had eaten away the upper part of the temporal bone but had not entered the middle-ear space. It had made its way to the surface through the posterior wall of the meatus. The case was published many years ago; and since then he had seen in the literature other cases quoted every few years. He had no doubt that such primary cholesteatomata did exist, quite apart from middle-ear suppuration.

Mr. C. S. Hallpike said that he thought this still difficult subject was now capable of considerable clarification. It was quite true that in the temporal bone one did encounter a number of epithelial tumour-like masses, which had nothing to do with the middle ear at all and which were, on the whole, curiosities of otological practice. What was left were these other epithelial masses, which always arose from the middle ear. The notion that they necessarily arose at some time from the external ear was, he would have thought, quite discredited. In the course of examining histological preparations of the temporal bone he had encountered in the attic little masses of epithelial material unaccompanied by any evidence of suppuration or by perforation of the tympanic membrane, and on one or two occasions he had seen in such cases, without deafness or perforation, large cholesteatomata filling the attic. These, he would have thought, were without doubt an early stage of the attic cholesteatoma with perforations with which they were so familiar. This condition arose in the middle ear and should be called middle-ear cholesteatoma.

The question which remained was whether it should be considered primary or secondary. He did not think there was very much to discuss on that point. Something must cause this proliferation of epithelium and therefore it was secondary.

As to the cause itself, it was most likely from what they knew of faulty mastoid pneumatization, that this region of the middle ear was irritated and caused to proliferate by some infection in early childhood or by some defective aeration of the middle ear, as the President had suggested.

Mr. G. Ewart Martin said that when he had been associated with the President during the period they had both worked with Logan Turner and J. S. Fraser many more cases of cholesteatoma were seen than nowadays. The number described as cholesteatoma was very large and there was no doubt that the flattened squamous cells in the attic proliferated, but was this proliferation due to infection or to something else? He felt there must be a cause and therefore these cases were not really primary but were secondary to something.

In recent years there were more such cases because of the routine examination of school children. He recalled that during the last war a man was examined and his hearing tested and passed as normal by the Medical Board. There was no history of pain in the ears at any time and examination at the Medical Board with an otoscope revealed nothing abnormal. One week later he reported with facial weakness on one side and constant headache. On examination there was a slight fullness of the attic.

It was decided to open the mastoid and the first blow of the chisel on the mastoid process brought everything away. There was the typical odour of cholesteatoma and examination proved this to be present. There must have been an infection of the lower part of the attic.

He was certain that a number of these cholesteatomata were associated with posterior marginal perforations which would again suggest differences in ætiology. He recollected one case in which a collection of cells in the attic became infected, and another with a chronic infection and a secondary proliferation with the characteristic smell and appearance.

Mr. I. A. Tumarkin said that he had not changed his opinion during the years since he wrote his original paper, which he would summarize as follows: There is only one type of normal mastoid, namely, the completely pneumatized. The so-called sclerosed mastoid is really non-pneumatized—i.e. it has failed to develop the normal air-cell system. The most important cause of this failure is latent mastoiditis associated with gastro-enteritis in nurslings. In this condition, the mucous membrane of the tympanic cleft has become in some way devitalized and so, in later life, is predisposed to break down under the impact of an infection.

There are two types of middle-ear mucosa—the tympanic mucosa covered by ciliated epithelium, and the epitympanic covered by squamous epithelium. These two types behave in different ways. The ciliated epithelium gives rise to the mucopurulent type of otitis media, often associated with nasopharyngeal disease. The squamous epithelium tends to proliferate and form squames. These squames are responsible for all the different pathological conditions found in the chronically infected mastoid. When the process is extremely slow it produces the so-called primary cholesteatoma, a laminated, pearly encysted mass.

At the other extreme—with active infection—bone destruction with formation of granulations and polyps is found. A more copious exudate occurs and this has two consequences. Firstly, the drum is perforated and secondly, the squames never have time to organize into typical laminæ. At most a whitish detritus is found. This is the condition which the President has so aptly designated Cholesteatosis and it accounts for all the conditions under discussion. It is always possible at operation to find some degree or other of cholesteatosis and often a mastoid exhibits different stages in different parts.

In acute suppurative otitis media, there is a stage *before* the drum perforates and a stage after perforation. These are not two separate entities—they are merely stages in a single pathological process. Similarly the existence or not of a perforation with overt discharge does not justify the description of primary or secondary cholesteatoma as separate entities.

Mr. I. B. Thorburn wished to suggest a practical clinical classification for these cases which he personally had followed in trying to design suitable operative treatment for them. There was a type of cholesteatoma which seemed to invade widely through the middle ear and mastoid space, and for that type one had to resort to a meticulously thorough mastoid operation. There was another common type where with the help of magnification it could be seen that the tympanic cavity had successfully walled itself off from the disease, either by granulation tissue or by new membrane formation. In such cases there could be an intact ossicular chain and a functioning tympanic membrane even though the head of the malleus and part of the incus were destroyed. A radical mastoid operation was not indicated but an epitympano-mastoidectomy would control the disease and give a much better functional result.

Miss Winifred Hall said that she had never felt very happy about the theory that non-pneumatization of the mastoid was due to a developmental failure. That was merely begging the question. Bony sclerosis was the response to infection, and infection in the infantile mastoid could occur so early—even in the first week or two of life, be so transient, and disappear without leaving any outward sign of its occurrence. One should not ignore the possibility of an unobserved or forgotten infection being the primary cause of a sclerotic bone. Having seen several hundreds of infants with otitis media, she thought this the most likely explanation both of so-called failure to pneumatize, and of so-called primary cholesteatomata.

She could not agree with the statement that the mastoid process and air cells were not fully developed before 2 to 3 years of age—this is disproved by operative findings which commonly show at all events partial pneumatization at 2 or 3 months of age, while complete pneumatization has been seen by 7 months. The process itself is present, though small, at birth.

Referring to established cases of cholesteatoma, Miss Hall commented on the frequent failure of radiological examination to help in diagnosis, particularly of early cases.

The President, in replying to the discussion, said that the question had arisen as to the bilateral occurrence of this condition. Of course it was quite commonly bilateral. They must all have seen many cases in which bilateral cholesteatosis was present. A diffuse cholesteatosis was quite commonly met with.

As to Mr. Watson-Williams's point about the etymology, he thought it was quite legitimate to think of the condition as a process, a continuing process, and the suffix "osis" would bear such an interpretation.

Clinical Section

President—W. A. BOURNE, M.D.

[*October* 14, 1949]

Sternal Secondary Deposit of Breast Cancer Treated by Radium Implantation. Patient Well Twenty-four Years Later.—W. SAMPSON HANDLEY, M.S.

Mrs. R., now aged 82.

Was operated on for left breast carcinoma by Miss Aldrich-Blake in 1918. In 1925 a prominent swelling 2½ in. in diameter appeared over the junction of the first and second pieces of the sternum and Dr. Helen Chambers referred her to me for radium treatment. Six tubes of radium bromide totalling 275 mg. were implanted in a circle round the swelling, and tubes of 50 and 25 mg. in its soft centre, for twenty-four hours. Within a few weeks the swelling disappeared, and pain ceased. Telangiectases appeared over the treated area. In 1943 a small skin nodule in the area was successfully treated by X-rays by Dr. D. W. Smithers. I am indebted to him for an X-ray showing recalcification of the softened sternum (Fig. 1).

At present, October 1949, this lady is perfectly well, and her voice may occasionally be heard on the radio.



FIG. 1.—Radiograph taken by Dr. D. W. Smithers in 1943, showing recalcification of the upper part of the sternum, indicated by the arrow. The lower part of the sternum shows some senile rarefaction but its outlines are well defined and anatomically normal. There is calcification of some of the costal cartilages.

Dr. G. E. Vilvandré said that the present result in this case was obviously excellent.

The action of stilbœstrol in these cases was worthy of discussion, and I have seen some cases and others have been described by Dr. Connell of Liverpool where bone recalcification had taken place to an extraordinary amount in ribs, humerus, pelvis, which had previously been studded with cancerous growth. Pain had ceased and general improvement followed.

One of the earliest sites of secondary deposits from the breast was in the pelvis, especially in the rami of the ischium. Patchy translucence of varying degree revealed secondary deposits and in carcinoma of the breast the pelvis should always be X-rayed.

A Dysplastic Lymphangiectatic Condition of the Left Hand and Forearm and Right Foot and Leg of a Little Girl, with Enchondromata or Cysts in Phalanges of the Affected Extremities.—Surgeon Commander M. A. RUGG-GUNN, R.N., M.D.; W. W. WOODS, M.R.C.S., L.R.C.P.; and F. PARKES WEBER, M.D.

M. R., a Singhalese girl, aged 4½ years. Normal birth.

Was brought in June 1949 as an out-patient to the Royal Naval Hospital, Trincomalee, Ceylon, because of a peculiar enlargement of the left upper limb and the right lower limb from the elbow and knee downwards. According to the parents this enlargement was present at birth and since then has increased only in proportion to the general growth of the body. At about the fourth month a vesicular eruption appeared on the affected parts; this disappeared, but has reappeared for periods of a few months at a time ever since; there is no accompanying itching. There is no parental consanguinity, nor is there any relevant family history, especially in regard to deformities. The child is the youngest of three girls, one boy having died at 4 months of pneumonia. The mother had one miscarriage.

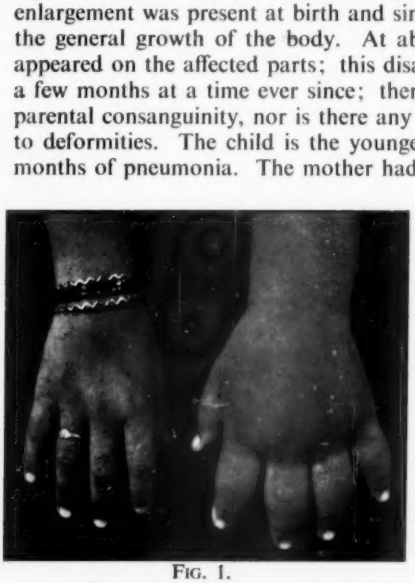


FIG. 1.

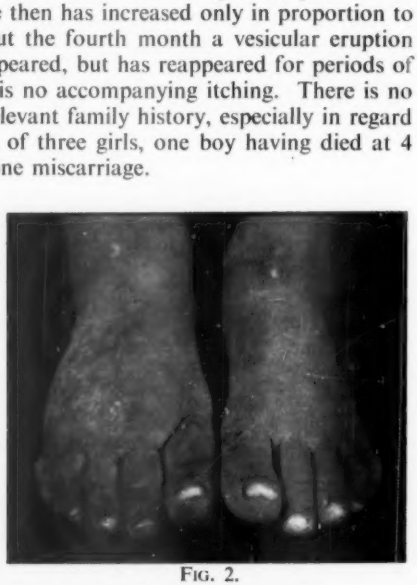


FIG. 2.

FIGS. 1 and 2.—Photographs showing the appearance of the affected extremities.

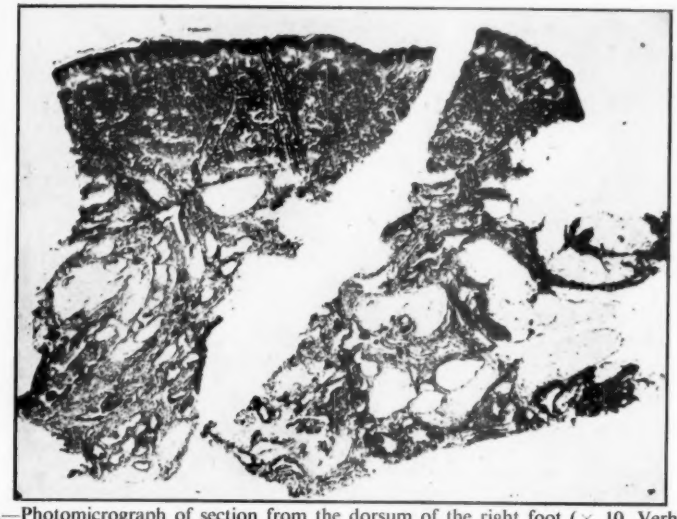


FIG. 3.—Photomicrograph of section from the dorsum of the right foot (× 10, Verhoef stain), showing widely dilated lymphatics and fibrosis in the subcutaneous fat. In the subepidermal part of the dermis are some slightly dilated lymphatics.

Present condition.—In the enlarged portions of the limbs (*see* photographs), by inspection, palpation and X-ray examination, the enlargement is found to be confined to the soft parts; there is no pitting on pressure (no œdema) and no discoloration of the skin beyond that which is connected with the occasional vesicular eruptions. There is apparently no difference in length of limbs, nor is there any noticeable difference between the radial pulses. Skiagrams show the presence of multiple enchondromata or cysts in some of the phalanges of the affected limbs; the rest of the skeleton is normal. General examination of the whole body shows no evidence of any other abnormality; no suggestion of sarcoidosis or xanthomatosis, though the blood serum cholesterol was high, namely, 500 mg.%. No enlargement of liver, spleen or superficial lymph glands. Blood count: Hb 92%; erythrocytes 4,520,000; C.I. 1·0; leucocytes 7,400 (polys. 40%, lymphos. 54%, monos. 3%, eosinos. 3%). Blood urea: 30 mg.%. Blood serum calcium: 8 mg.%. Urinalysis showed nothing abnormal. Wassermann reaction negative. The general health appears normal.



FIG. 4.

FIGS. 4 and 5.—Skiagrams showing enchondromata or cysts in some of the phalanges of the affected hand and foot. (*See* overleaf Fig. 5.)

In a specimen excised from the dorsum of the right foot Mr. W. W. Woods reports that there is conspicuous dilatation of lymphatics in the subcutaneous fat; some of the lymphatics have muscular walls; there is pronounced fibrosis, with elastosis, in the subcutaneous fat; there is neither œdema nor inflammatory infiltration in the subcutis or dermis; in the subepidermal part of the dermis are a few slightly dilated lymphatics.

Remarks.—There can be no doubt that the condition is a developmental (congenital) lymphangiectatic dysplasia of the affected parts (without œdema). This diagnosis is

endorsed by Dr. W. Freudenthal. The occasional vesicular eruptions are perhaps connected with the subepidermal dilated lymphatics. The multiple cyst-like appearances in some of the phalanges of the affected hand and foot (a biopsy was impossible) are most probably due to enchondromata. An analogous condition of hæmangiectatic dysplasia of extremities is sometimes associated with enchondromata (? cartilaginous hamartomata) of the Ollier type of dyschondroplasia, constituting the so-called Maffucci's syndrome (*see* Carleton, Elkington, Greenfield, and Robb-Smith, *Quart. J. Med.* (1942) **11**, 203).

Dr. G. E. Vilvandré, when asked the condition of the terminal phalanges and metatarsals, suggested that they were most probably numerous enchondromata.

Dr. A. Elkeles said that the cystlike appearances in the phalanges, as seen in the radiographs of hands and feet could be interpreted as enchondromata. The phalanges were notably affected in this type of dyschondroplasia. Dr. Parkes Weber was able to exclude sarcoidosis and xanthomatosis in which similar radiological bone changes might occur. Some years ago he had observed an extensive hæmangioma in a child, affecting one lower arm, wrist and hand. Radiographs of this region showed concomitant involvement of the bones by hæmangioma. In the present case the cystlike bony lesions were also confined to the areas affected by lymphangiectatic dysplasia. Since the basic pathology of hæmangiectatic and lymphangiectatic dysplasia was similar, it might be suggested that the cystlike lesions in the phalanges of the present case could also be explained as an extension of the lymphangiectasis of the surrounding soft tissues.



FIG. 5.

Mr. A. Dickson Wright said that there was a close similarity between the behaviour of the lymphatics and the veins in the matter of congenital deviants. The compact lymphangioma of the neck resembled the circumscribed angioma and in the arms and legs there occurred diffuse lymphangiomata resembling those of Weber's disease except in the contents of their spaces. It would be interesting if this case showed that in the formation of enchondromata of the phalanges there was a still further analogy in the two diseases.

FIGS. 4 and 5.—Skiagrams showing enchondromata or cysts in some of the phalanges of the affected hand and foot. (*See* Fig. 4 on previous page.)

Diffuse Adenomatosis of the Trachea.—J. A. TUTTON, M.B., B.Chir. (for N. LLOYD RUSBY, D.M.).

G. C., male, aged 54. Labourer.

History.—Cough with 1 oz. of mucopurulent sputum since 1933 following pneumonia on the right side. January 1944: Hæmoptysis whilst at work. Since then has had attacks of hæmoptysis every two or three months. June 1949: 10 oz. hæmoptysis. For four years has had dyspnœa on exertion. Weight: For the last ten years weight has been steady at 10 st.

Past history.—Left antrostomy in 1930 for hæmantrum following repeated epistaxis.

Past investigations.—Bronchoscopy 1945: ? Tuberculous tracheobronchitis. (Description corresponds closely to present appearance.)

On examination.—Apyrexial. Diffuse nævi over face and trunk. Two polypoid angiomata on chest. Otherwise general physical examination revealed no abnormality. Blood pressure 140/95.

Investigations.—X-ray of chest—cystic condition right upper lobe confirmed by tomography. X-ray of sinuses clear.

Laryngologist's report.—"No cause for bleeding found in upper respiratory tract. Lesions well seen in trachea with laryngeal mirror."

Sputum persistently negative for tubercle bacilli and neoplastic cells. Full blood count normal including clotting and bleeding times. W.R. negative.

Bronchoscopy (30.9.49).—Cords normal. Trachea normal until about two-thirds of it had been inspected when the mucous membrane became hypertrophic and the change was apparent on both sides, left more than the right, and was continued into both main bronchi and appeared to terminate rather abruptly on the left side at the left upper lobe, but rather less abruptly on the right side at the right middle lobe level. The craggy rugose appearance suggests a condition of diffuse papillomatosis.

No bleeding was excited. Mucosa was more injected than normal. Biopsy taken. *Section* shows normal mucous membrane.

The most likely diagnosis in view of intact mucous membrane is of a diffuse adenomatosis of the trachea.

The association with repeated epistaxes, hæmantrum and angiomata of skin is interesting. It is possible that the circular shadow seen in the right upper lobe may be the remains of a blood cyst.

Fibrocystic Disease of Pancreas. Bilateral Bronchiectasis. Cirrhosis of Liver.—D. GERAINT JAMES, M.R.C.P. (for J. W. CROFTON, M.R.C.P.).

G. R., page boy, aged 15 years.

Previous history.—Frequent chest colds each winter since age of 3 years. Aged 9 years: In hospital for tooth extraction—enlarged liver noted. Weight 3 st. 7 lb. Aged 11 years: Illness (? jaundice) with pale stools, since when stools have continued to be pale and offensive, and he has failed to grow or to develop. Since this time chest colds have been more severe. Aged 14 years: Clubbing of fingers noted by

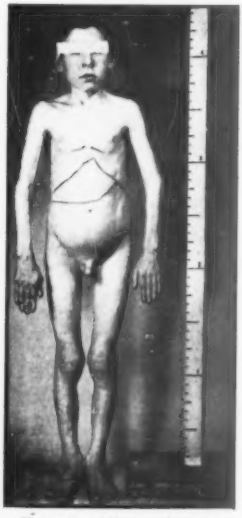


FIG. 1.—Illustrating lack of growth and genital development, enlarged liver and clubbing.



FIG. 2.—X-ray of chest, showing "snow-flake" mottling of both lung fields.

school nurse. Aged 15 years: Five months ago, severe bronchitis with purulent sputum and marked dyspnœa.

Family history.—Father and mother well. 1 brother died of bronchopneumonia, aged 2½ years.

On examination.—Looks 9 to 10 years old. Ht. 4 ft. 4 in. Wt. 3 st. 10 lb. No signs of puberty (Fig. 1). Very cyanosed, and quite marked clubbing. Looks ill ; markedly dyspnœic; and febrile. Chest, fixed, with Harrison's sulci. Harsh breath sounds with numerous added sounds throughout both lung fields (Fig. 2).

C.V.S. N.A.D.

Abdomen: Enlarged liver, 4 fingerbreadths below costal margin in mid-clavicular line, firm, not tender. No splenomegaly. Both testicles undescended. No pubic hair.

Investigations.—Hb 100%; W.B.C. 16,000. E.S.R. 72. Serum bilirubin 1·1 mg./100 c.c. Plasma proteins 7·7 grammes %. Albumin 3·1 grammes %. Globulin 4·6 grammes %. Thymol turbidity 2·5 units. Colloidal gold 0. Blood calcium 11·1 mg.% Serum phosphate 4·7 mg.%. Chest X-ray shows diffuse "snow-flake" mottling throughout both lung fields. Ossification centre for trochlea not yet present. No evidence of rickets. Sputum showed mixed bacterial flora, including *Strep. viridans*, Neisseria, diphtheroids. Mantoux negative 1 : 100, old tuberculin. Duodenal intubation performed; juice showed absence of trypsin. Stools putty-like. On standard fat balance of 50 grammes intake daily for four days, fæcal fats (daily average) were 13·8 grammes. This shows 73% fat absorbed. On diet of 100 grammes protein daily, there were 2·2 grammes of nitrogen in the fæces daily, and 5·4 grammes of nitrogen in the urine daily. This showed a protein absorption of 89% and utilization of 50% protein.

Progress and treatment.—The severe pulmonary infection was controlled by 1,000,000 units of penicillin intramuscularly daily, and also inhalation penicillin.

The diet was increased to a highly nutritious diet with added vitamins, with a resulting weight gain of 6 lb. in the first month, and his general condition immensely improved.

Dr. J. W. Crofton: The absence of duodenal trypsin is strong evidence that the case is one of fibrocystic disease of the pancreas. It is unusual in that the boy has survived to the age of 15 and that there was no clear evidence of disability before the age of 3. He has so far reacted well to dietetic treatment and to penicillin treatment of the purulent bronchitis.

Toxic Thyroid Adenoma. Generalized Osteoporosis with Collapse of Some Vertebræ.—B. GOTTLIEB, M.R.C.P.

B. V., spinster, aged 47. Housekeeper.

Menopause at 42 years.

Admitted St. Mary Abbots Hospital 30.3.49. Discharged 9.5.49.

History of thyrotoxicosis.—Thyroid gland enlarged for at least thirty years. Disliked warm weather for many years. Nervous and excitable at least eighteen months. Lost 2½ st. in weight past three months. Shortness of breath on exertion with œdema of feet two months. Vomiting three weeks.

On examination.—Weight, 8 st. 4 lb. Heart rate 104, extrasystoles. Tremor of fingers. Large thyroid adenoma involving right lobe and isthmus.

Investigations.—1.4.49: B.M.R. + 65·6%. 5.4.49: Radio-active iodine test—4·7% excreted in forty-eight hours. 1.4.49: X-ray chest—retrosternal prolongation of thyroid.

Treatment.—16.4.49 – 9.5.49: 400 mg. methyl thiouracil daily. 9.5.49 – 2.6.49: 200 mg. methyl thiouracil daily.

The methyl thiouracil was given preparatory to thyroidectomy, but patient declined operation subsequently.

Progress.—Thyrotoxic symptoms and signs lessened.

Gained 1½ st. in weight. B.M.R. 2.9.49: + 13·5%.

History of osteoporosis.—Ten years back felt "weak and cold" at times following exertion.

End of June 1949 (after control of thyrotoxicosis) developed severe pain in back radiating along the left sciatic nerve.

July 1949: Pain lower dorsal spines radiating along right subcostal margin. Pain persistent since then and back has gradually become bent.

Readmitted 24.8.49.



FIG. 1.—X-ray lumbar spines showing osteoporosis with collapse of some vertebræ.

On examination.—Height 5 ft. 3 in. (5 ft. 5 in. one year previously).

No gross thyrotoxic signs. Thyroid adenoma. Heart rate 80, regular.

Spines: Tender lower dorsal and upper lumbar vertebræ. Rigidity of spines. Kyphosis of dorsal spines.

Investigations.—24.8.49: Radiography bones: Generalized osteoporosis all bones especially vertebræ with collapse of some dorsal and lumbar spines (Fig. 1).

Sacro-iliac joint spaces not seen.

16.9.49: Serum calcium 10·1 mg.; serum phosphates 3·8 mg.; and serum alkaline phosphatase 14·5 units/100 ml.

Fæcal fat estimation.—12.10.49: Total fat 7·68 grammes, split fat 7·13 grammes, and unsplit fat 0·55 gramme per 100 grammes dried fæces.

Comment.—The association of osteoporosis with thyrotoxicosis has been frequently reported but Bartels and Haggart (1938) were able to find only 5 cases in literature where the osteoporosis was sufficiently severe to cause spontaneous fractures. Although these conditions may coexist there is no definite evidence that the thyrotoxicosis is actually responsible for the osteoporosis. Several observers have reported no improvement in the osteoporosis despite thyroidectomy and Hunter (1935) found that the negative calcium balance persisted in his case two weeks after thyroidectomy, and osteoporosis was unchanged one year later. In my patient symptoms and signs due to the osteoporosis first became obvious only after thyrotoxicosis was controlled by methyl thiouracil.

The cause of the osteoporosis has not been determined in these cases. Although hyperparathyroidism has been suggested as a possible cause, the serum calcium and phosphorus have not been raised in previously reported cases and they were normal also in my patient. Nor was there any evidence of steatorrhœa in any of these patients.

As regards treatment it is proposed to perform a thyroidectomy on this patient because of marked retrosternal prolongation and to avoid a possible relapse of the thyrotoxicity and to examine the parathyroid glands during the operation. Large doses of vitamin D and calcium will be tried subsequently, although McCance (1947) mentions osteoporosis associated with thyrotoxicosis as being resistant to vitamin D. At the same time an orthopædic appliance will be used to prevent further deformity of her spine.

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Meningococcal Encephalopathy.—M. N. PAI, M.R.C.P.

Male, aged 32, single.

1940: Since an attack of cerebrospinal fever he has suffered from defective memory, confusion, loss of initiative, mild "depression", and changes in personality. He has become morbidly passive and docile, timid and has been unable to hold down a job for longer than a few days. On account of long spells of unemployment he has become completely dependent on his elderly parents.

1947–48: For fifteen months in hospital in the Midlands and was treated with electric convulsion therapy without any improvement at time of discharge.

Previous history and personality.—No family history of mental or nervous disorder. According to his school report he was a boy of good intelligence, of good character and was always trustworthy, polite and friendly with his fellow scholars. Prior to the meningitis for nine years he had no unemployment. He had even taught himself several foreign languages.

1949: *Condition on admission.*—Well nourished. C.N.S.: NAD. *Mental state*: Mild euphoria, lack of spontaneity and perseveration; can converse in French, Italian, Polish, Spanish and Hindustani, but gets easily confused. His memory for past events is very defective and he has difficulty in forming new associations of ideas and in planning ahead. *Change in personality*: Previously a good "mixer", well behaved and well mannered, he has now become careless in habits, untidy in dress, diffident and childish in behaviour. Diminished libido, impotence and lack of interest in the opposite sex has been followed by the development of an obsessional urge to interfere with young boys.

Investigations.—Wassermann reaction negative. Electro-encephalogram: "Abnormal. This record suggests a diffuse organic deterioration, mainly in the temporo-parietal areas."

DISCUSSION

The intellectual, social, economic and moral deterioration as well as tendencies to prolonged invalidism present in this patient are prominent features of meningococcal encephalopathy (Pai, 1944, 1945, 1946). This condition is easily differentiated from schizophrenia by the absence of evidence of thought disorder, hallucinations and delusions and from post-contusional states by the absence of irritability, headaches, aggression and paranoid reactions. Neurosis is excluded by the absence of psychological causes and of personal motives.

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Torticollis and Tremor of Head of Five Years' Duration. (*Wrongly Diagnosed as Functional in Origin*).—M. N. Pai, M.R.C.P.

Male, aged 61. Long-distance lorry driver for thirty years.

1944: Sudden onset of acute pain in the neck, worse after movements of head and neck. Despite physiotherapy for nine months pain persisted and patient gradually developed right torticollis and an involuntary tremor of the head. Continued to drive a lorry at night.

1948: Tremor of head and neck became incessant and difficult to control; the lower jaw began to droop and he had difficulty in speaking, eating and drinking. On account of the severity of his symptoms, which were still considered functional, he was recommended for urgent in-patient treatment at a neurosis centre.

1949: *Condition on admission.*—Thin, poor physique, looks older than his age. Marked kyphosis with head bent forwards, the chin almost touching the chest wall. The tremor of the head has two components:

(1) Lateral tremor consisting of a quick movement from right to left and a slow release movement in the reverse direction.

(2) To-and-fro or antero-posterior tremor consisting of a slow, strained forward movement and a quick backward recoil.

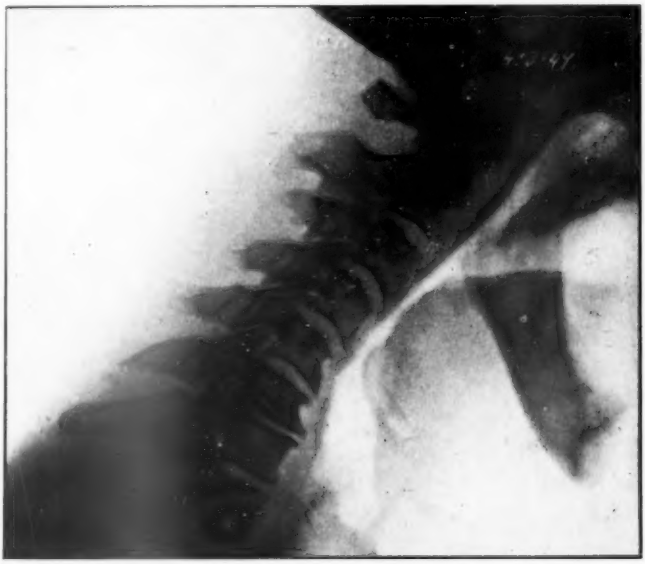


Fig. 1.—Showing advanced osteoarthritis of cervical vertebræ and degenerative changes in the discs, especially between C5 and C6 and between C6 and C7.

Continuous rolling movements of the tongue. Right torticollis and hypertrophy of the right sternomastoid. Hypertrophy and spasm of right trapezius and right semispinalis capitis. Grating audible in the neck and crepitus felt in the region of C5 and C6. Central nervous system: Marked retinal arteriosclerosis, left eye amblyopic, vision being less than 6/60. General medical examination revealed nothing else abnormal.

Investigations.—W.R. negative; total blood counts and sedimentation rates within normal limits. Hb 100%. Colour index = 1·0. X-ray of cervical region: Advanced

osteoarthritis and degenerative changes in the discs between C5 and C6, and between C6 and C7 (Fig. 1). Appearances compatible with an old crush fracture of C6. Sacral region: Osteitis deformans.

Discussion

This patient well illustrates how tremor of the head may be caused by physical conditions. For ordinary activities central vision is essential but for driving any vehicle good peripheral vision is necessary. The greater the speed of a vehicle the greater is the need for good vision. Being almost blind in his left eye he was therefore compelled to bring the right field of vision towards the middle in order to avoid objects moving from his left side. This frequent turning of the face to the left led to hypertrophy of the right sternomastoid. Each time the face was turned to the left the right trapezius and the right semispinalis capitis pulled the head backwards and to the right, since the right shoulder was fixed during driving. These alternate movements led to hypertrophy of the muscles and caused the lateral tremor.

For thirteen years he was on night duty which involved driving in the blackout continuously for ten to twelve hours or longer. This required craning his neck forwards but on account of the pain due to degenerative changes in the vertebræ and discs the head was quickly withdrawn. These two movements resulted in the anteroposterior tremor. In 1944 he apparently sustained a crush fracture of the body of C6.

No adequate explanation of the movements of the tongue can be given. Normally the upper dental arch is wider than the lower so that the upper incisors and canines overlap the lower ones. The opposed dental arches form a strong fortress which protects the surface of the tongue from external damage. In this patient owing to the large size of the mandible the lower dental arch is wider than the upper and he has difficulty in keeping his mouth closed. The movements of the tongue are, perhaps, nature's attempts to protect the surface of the tongue.

Psychiatric investigations have not revealed any psychological factors or personal motives to account for the tremor.

Five cases of Rheumatoid Arthritis: Extraordinary Therapeutic Results by Procaine Injections in Specific Objectively Located "Myalgic Spots."—M. G. Good, M.D. A report of these cases has appeared in *Zeitschrift für Rheumaforschung*, 1950, Vol. 9, Heft 1–2, Jan.–Feb. (in English).

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Section of the History of Medicine

President—E. Ashworth Underwood, M.A., M.D., D.P.H.

[*November* 2, 1949]

Théophile de Bordeu: An Eighteenth Century Pioneer in Endocrinology

By A. P. Cawadias, O.B.E., M.D., F.R.C.P.

Théophile de Bordeu, the great mid-eighteenth century Montpellier physician, developed in his work all aspects of Constitutional Medicine, and in doing so introduced into medical thought the conception of internal secretions as pointed out by H. Grasset [1], and by Max Neuburger [2]. In this paper I shall endeavour to study more completely the personality of Bordeu, and to show his role in the stream of thought, which from the Hippocratic humoral conceptions brings us to contemporary Endocrinology. This study will help us to consider the principles of Endocrinology, because we cannot understand this fascinating branch of Medicine simply by absorbing the innumerable papers which are being published at an increasing rate. We can read ourselves into ignorance and stupidity if we do not seize the directive lines of scientific thought as shown through history. We have to think of our problems more and more closely with the help of the great intellects that have thought about them in the past. Scientific thinking—the basis of Science—can only be historical thinking.

Life and Background [3, 4, 5]

Théophile de Bordeu (Fig. 1) was born in 1722 and died in 1776. He thus belongs to the mid-eighteenth century, the times of Louis XV in France, and George II in England. His French contemporaries were Boissier de Sauvages, Senac, Lorry, Barthez, Tronchin. Amongst his



Fig. 1.—Théophile de Bordeu (1722–76)

From Rolleston: The Endocrine Organs in Health and Disease, 1936, Oxford University Press.

British contemporaries—a more brilliant galaxy—were Pringle, Heberden, Fothergill, Lettsom, Erasmus Darwin, Withering.

His life can be divided into three phases, that of preparation, the "Wanderjahre", and the Paris period.

The period of preparation (1722–1743) was lived in his native land. He was born at Izeste near Pau, a scion of a great family, and the son of a distinguished physician, Antoine de Bordeu, state councillor, superintendent of the waters of Aquitaine, and one of the pioneers of Medical Hydrology. This Antoine de Bordeu, a cultivated gentleman and keen naturalist, was the first teacher of his son Théophile and developed in him the power of observation and of thinking, accompanying him on his walks and excursions in the beautiful surrounding country. A general, principally classical, education was given to Théophile de Bordeu in the college of the Jesuits of Pau and of the Barnabites of Lescar, and at the age of 17 he entered the medical school of Montpellier.

Montpellier is, with Salerno, the school that introduced Medicine into the West. Although already going strong in the eleventh century, it maintained its supremacy until the beginning of the nineteenth century, and in Bordeu's day was at its zenith with teachers such as the great clinician, Fizes, and the founder of modern Nosology, Boissier de Sauvages. An essential feature of that great school was its faithfulness to the Hippocratic tradition, that is, of the method of clinical observation combined with the cult of general ideas. Montpellier was the real civitas Hippocratica, and even when I was there as a student we could read everywhere "Nunc Monspelierensis Hippocrates". Bordeu applied himself, particularly, to Anatomy, which was in those days the only discipline embodying precise scientific method. He followed the clinical teachers who took the students into the homes of the poor patients—a special method of Montpellier, the real Hippocratic method of clinical teaching—but also frequented the St. Eloy Hospital open to all students. He obtained his M.D. in 1743 at the age of 21.

The "Wanderjahre" (1743–1752).—This interesting feature, which is often encountered in the lives of many clinicians, lasted from Bordeu's twenty-first to his thirtieth year. In the first four years after his graduation he remained between Pau and Montpellier, acquiring clinical experience through an extensive practice and visits to hospitals, and continuing his anatomical and physiological studies. He next went to Paris where he stayed another four years studying a more extensive clinical material in the hospitals, working in surgery as assistant to L. J. Petit, absorbing with enthusiasm the first elements of the new science of chemistry, with the help of François Rouelle [6], and acquiring the experience of the world—indispensable to the formation of a clinician. He then returned to Pau as demonstrator of Anatomy and superintendent of the mineral waters of Aquitaine. There he remained for two years, continuing his clinical and physiological work and studying the clinical effects of the mineral waters, after which time he went back to Paris. His return was preceded by the publication of his masterpiece "On the Position of the Glands and Their Function".

The Paris period (1752–1776) was the last phase of his life, extending from the time of his finally settling in the capital of France at the age of 30 until his death at the age of 56.

Thus, Paris was the great theatre of action of Bordeu, but, although in the Paris environment, he remained a Montpellier physician, for, as with so many great men, his work was really accomplished before 30 and the rest of his life was a simple elaboration of the intuitions of his youth on the shores of the Mediterranean. In fact, his essential role was to bring to the Faculty of Paris, stagnating in a scholastic pseudogalenism, the vivifying Hippocratic spirit of Montpellier. Later, other Montpellier physicians, like Pinel, did the same and helped to make the great clinical school of Paris which we all admire to-day.

In the French capital Bordeu rapidly acquired the position of one of the few leading physicians, but not without struggle as he met with a bitter and passionate opposition.

He became the physician to the rich and powerful, including the King's favourite, DuBarry, and, although not appointed as physician to the King—Louis XV did not fill this post after the death of Senac—he was called in consultation during the King's last illness. In the midst of this extensive practice, together with his work at the Charité Hospital, Bordeu continued his researches and writings, but all his publications were now merely an elaboration of the material collected in his early days in the South. Practice and research were done within the frame of an intense social life, in the brilliant Paris of that period. Bordeu was a friend of the encyclopædists, of Diderot, of d'Alembert, he frequented the salons of the Duke of Chartres, of Madame Montesson, and he was intimate with the famous Mademoiselle de Lespinasse. He loved the Comédie Française and was often seen backstage at the Opera. He remained a bachelor, living with Louise d'Estrées, but this did not hinder him from indulging in numerous amorous intrigues, quite in accordance with the custom of the period. He burned, alas, the candle at both ends, and exhaustion caused his early end: he died of apoplexy—as had been predicted to him by his teacher, Fizes, many years before.

The personality of Théophile de Bordeu was that of a high-class clinician and we can reconstruct it through his published works, and, principally, through the testimonies of his contemporaries. He showed that combination of scientific and artistic qualities which characterizes the Mediterranean clinician. He had the keenness of observation and the clarity of reasoning bound up with the luminosity of the southern landscape and the sharp lines of its horizon. He possessed to a high degree Intuition, that faculty more artistic than scientific, which in Medicine consists in seeing the patient from the inside, in assessing rapidly his total personality, physical and mental, and thus in understanding the whole problem, because patients are not Hearts or Stomachs but are human problems. As every human problem, even though we may be presented with only one aspect of it, involves the whole man and his environment, Intuition becomes the great clinical faculty, allowing for a more efficient human action such as cannot result from a simple addition of signs and laboratory tests. Above all, Théophile de Bordeu possessed that universality and tendency towards comprehensive and general ideas that has always been the essential feature of Mediterranean thinkers.

For the understanding of thinkers like Bordeu we must distinguish the Mediterranean from the Nordic spirit. The Mediterraneans, happy in their beautiful climate and men of few material needs, were stimulated through their leisure towards the accurate observation of Nature, towards precise, although abstract thinking for the conquest of the spiritual world. The Nordics, struggling in their hard climate, have been directed towards defence against adverse natural conditions, and thus towards the conquest of the material world. Religion and Philosophy came from the Mediterranean: machinism is a Nordic product. Mediterranean Medicine is a medicine of great intellectual synthesis and of intuitive understanding. Nordic Medicine is a medicine of experimentation, of mechanical application and of analytical reasoning. The typical Nordic physician is a man of deep specialized knowledge and master of technique. The typical Mediterranean physician is an inspired clinician, a man of broad vision, of wide culture and of varied activities.

Medicine in general needs these two approaches, but we have the tendency to follow the Nordic more than the Mediterranean approach. This has been a mistake, and for that reason some contact with Mediterranean intellects like that of Bordeu becomes necessary. The slick ingenuity of a single track mind makes for great and spectacular technical developments but the rich and fruitful intuitions of a universal mind will always prove of greater service to humanity.

The Doctrine of Internal Secretions

The essential work of Bordeu has been the development of the principles of Constitutional Medicine, as introduced by Hippocrates. These principles are : (*a*) Principle of Integration in health and disease ; the organism is a whole, and acts as a whole ; disease is a total, "psychosomatic" reaction. (*b*) Principle of Ætiological constellation. Disease represents the reaction of our φύσις, our constitution to adverse environmental factors, and thus, it is determined by a combination of various environmental factors and individual constitutional features. (*c*) Principle of Natural healing powers. Cure is based on the natural, self-regulating power of the organism, on its endeavour to restore its balance disturbed by the adverse environmental factors.

It is by thinking and developing the first of these principles, that of integration, that Bordeu discovered the function of internal secretion. Before Bordeu physicians were divided in their ideas about the mechanism of integration of the organism. Many accepted the conception of Alkmeon (sixth century B.C.), according to which the organism was a whole and acted as a whole, because all its parts were integrated by the brain. Others accepted the Hippocratic conception of humoral (or chemical) integration, according to which it was the humours of the body that effected the correlation of all parts and thus allowed the organism to act—and to react—as a whole. Bordeu accepted that both these mechanisms existed normally, and the conception of this double mechanism of integration (nervous and chemical) remained in our science until a few years ago, since when physiological researches, such as those of Sir Henry Dale, allowed us to unite these two mechanisms into the conception of neurohumoralism.

In thinking of the mechanism of nervous integration Bordeu hit on the doctrine of cerebral localization.

" We are led to believe that every organ has an impulse coming from the brain, which itself is so constituted that its different parts have different functions and control the corresponding nerves, so that what takes place in the organs is but the effect and image of what first occurs in the brain. In a word, we believe that functions first begin in the brain, which is divided into as many compartments as there are organs, and it is so constructed that it stimulates this or that organ, and regulates this or that function through what occurs at the origin of the nerves of the organ; this may be but a more or less pronounced action of a certain part of the blood vessels." (*Œuvres complètes*, tome 1, pp. 201-202).

In his elaboration of the Hippocratic humoral mechanism of integration he is led to the conception of internal secretions. How is it that the humours correlate all parts of the body into a harmonious whole ? The answer is found in following passages of Bordeu's works.

" Each of the organs serves as a factory and laboratory of a specific humor which it returns to the blood after having prepared it within itself and imparted to it its own intrinsic character . . . . The blood has peculiar qualities which it has acquired in the tissues from where it comes. Every organ sends to it continuous emanations and thus the blood carries in its torrent extracts of all organs, which are indispensable for the life of the whole (*Œuvres complètes*, II, p. 942). The blood bears within itself extracts of all the organic parts, each of which is necessary to the well-being of the whole, and possesses specific qualities and properties beyond the reach of the chemist's experiments " (*Œuvres complètes*, II, p. 943).

Thus, Bordeu, developing the Hippocratic ideas, introduced into scientific thought the conception of internal secretion as of a general function, a function of all organs, all tissues, all cells. This conception was elaborated with great precision by Brown-Séquard and d'Arsonval (1891), but with the intense study of the specialized organs of internal secretion it was nearly set aside. We are returning to it. We know that all cells possess, to a more or less high degree, incretory function, and that the glands of internal secretion are simply an accumulation of cells possessing this function to a high and specialized degree. This is the basic principle of Endocrinology.

The Special Organs of Internal Secretion

The relation between the omnicellular incretory function and the special endocrine glands was not well understood in those days (and has, in fact, been only recently understood), but parallel with the work that gave us the omnicellular incretory function was proceeding work on special endocrine glands, and in this work, also, Bordeu played an important part.

The first organ studied as an endocrine gland was the testis. The experiments on human castration, and the differences of various features amongst the sexes, helped the ancient Greeks to accept that the "semen" played a great role in the development of masculine features and qualities, and this idea was embodied in the words of Aretaios, "The semen makes man".

Thomas Willis developed more fully this conception in his *de Cerebri Anatome* (1664), where he wrote that the blood receives from the genitals "certain particles imbued with a seminal tincture, which, carried back into the bloody mass makes it vigorous and inspires to it a new and lively virtue".

Bordeu goes one step further in this conception of internal secretion of the testis.

" The semen imparts a firm and masculine tone to all parts as soon as it can be drawn off and sent into the humours and solids by its natural organs. It sets a new seal upon the animalism of the individual, who is, in part, subject to the action of this creative liquor " (*l.c.* p. 842). . . . This liquor (semen) penetrates the mass of the humours. . . . It has the property of consolidating the parts and of nourishing them. It excites and stimulates all the fibres. It is the cause of that fetid odour exhaled from vigorous males. . . . In a word, it must be considered as a special stimulus of the machine which physicians have not sufficiently considered.

Apart from the general concepuon of the masculinizing action of the testicular internal secretion, let us note the detail of the determination by this secretion of the "fetid odour" of vigorous males. Testosterone stimulates the sebaceous glands, and of course the odour of the sebum secretions was more pronounced in the eighteenth century which was not distinguished by cleanliness.

Bordeu accepts what we call, to-day, the psychosomatic link through the endocrines—a notion developed in our day by our former president, Sir Walter Langdon-Brown. "The aura seminalis serves more than the other liquors as a link, or intermediary, between the body and the mind (*Œuvres complètes*, p. 959).

Next to the endocrine function of the testis, Bordeu points to the endocrine function of the ovary, and this, possibly, for the first time in medical thought, although the first description of the effects of experimental female castration was by Aristoteles. In describing these effects of female castration in fowls Bordeu adds, "These phenomena prove that females may like males, receive from the generative organs a vital impulse which stimulates and influences them. This is certainly true of women" (*Œuvres complètes*, p. 950).

From a nosological, or clinical, scientific point of view, Bordeu describes—this, also, I think, for the first time—the existence of a female eunuchoidism parallel to the well-known male eunuchism and eunuchoidism (*Œuvres complètes*, p. 950).

Further Work on Constitutional Medicine

Théophile de Bordeu elaborated the second Hippocratic principle, that of the Ætiological constellation. In the consideration of the external ætiological conditions he stressed the importance of the psychological and social factors, developing, thus, the "psychosomatic

principle". "Look for all factors", he writes in his *Maladies Chroniques*, "which bring the disturbance in the patient, particularly in chronic cases. Look, particularly, for the mental factors, frequently more potent, more difficult to ascertain, more important to consider." He also stressed the internal, constitutional, ætiological factor in disease.

We read in his *Recherches sur les maladies chroniques*:

" The physician must apply himself to know the temperaments that are the sources of many diseases. He must not devote himself entirely to the study of epidemics and diseases of certain countries while neglecting the study of the living body. It is less important to know which constitutions in the air determine the epidemics, than to know which temperaments can be affected. There are temperaments that fecundate easily the germs of the diseases. There are others that convert all diseases in those that are proper to them. This is demonstrated by the asthmatics or gouty, who show asthma or gout although pleurisy or angina reign in that epidemic."

There was a time when the ideas embodied in this passage were forgotten, but they have come into the foreground again, and the lines of Bordeu can be inserted in the most modern book of Pathology. And how about this . . .

"Why does the virus of smallpox not attack those who have already had this disease, although in the course of epidemics it penetrates into the blood mixed with the air that is breathed, the saliva, the foods . . . whereas, when inoculated in those who have not had smallpox it gives the disease. One must think that if this virus does not act, it is that it does not find in the body the favourable disposition, because this favourable disposition has been destroyed with the first attack of the disease. . . ." (*Recherches sur les maladies chroniques*. Edition Roussel, p. 89, xxxiii.)

In developing the third Hippocratic principle, that of the Natural Healing power which demands that the physician use methods which help the constitution in its fight against disease, Bordeu showed the importance of mineral waters in treatment. He thus became, with his father, a pioneer in Hydrology as well as in Endocrinology. His observations on the course of the disease in patients submitted to medical water cure at Bareges can be read with profit by modern hydrologists, particularly in days when we have a tendency to neglect that most valuable therapeutic method. He noted in some cases, particularly of rheumatism, an initial aggravation in the course of an hydromineral cure, and compared this aggravation to the "crisis" in acute diseases, and showed that like the crisis it heralded an improvement in the condition of the patient.

As a real Hippocratist he poured scorn and mockery on those who believe they can scarcely prescribe enough drugs nor order sufficient venesection, and who thus obstruct the Natural resistance. "It seems to me I hear Nature crying, 'Do not hurry, let me alone. The drugs that you cram into the body of the sick will not cure, it is I, alone, who cures. The moments in which you appear the most agitated are those in which I save myself most—if you have not taken away my forces. It would be better if you trust in me, abandoning all your doubtful remedies'."

I shall only touch the question of his elaboration of Hippocratic "physis" into the Montpellier "vitalism". Bordeu's work on this point seems to be highly speculative, but it has been the inspiration of the more precise work of Bichat.

Théophile de Bordeu did not limit himself to studying general pathology but made some important researches on special clinical problems, particularly on the pulse, and published an important work on this subject based on his observations in the Charité Hospital.

Discussion

Medicine is part of History, and History is continuity. The stream of scientific thought is continuous, and although in this continuous flowing we can note—often artificially—certain landmarks, we cannot speak of originators. We cannot cut into time. Nothing begins in the History of Science and when someone expresses an idea it is already in the air. Bordeu represents a landmark in the History of Endocrinology, in the same manner as Berchtold, Claude Bernard, Addison, Brown-Séquard, represent other landmarks, but we cannot call any one of them the father of Endocrinology. Questions of priority, naïve satisfactions of individual, national and racial prejudices go against the sense of History, which is the sense of continuity.

Even from that point of view, the role of Bordeu in Endocrinology has been discussed because, as Garrison [7] writes, "He was very close upon the modern theory of internal secretion and hormonic equilibrium, but as he made no experiments his ideas can be regarded as sheer theory only". But "Theory", which in the original Greek means the highest form of thinking, is the basis of scientific development. Science is not a mass of more or less connected technologies, but is a product of human thought. Observation and experiment are instruments of human thought, and are useless when divorced from thinking. We have forgotten that in our supermechanized days, and thus risk to merit the reproach of Nietsche

to his contemporary professors, who, "work hard day and night so that they may not have time to think". On this principle we should dismiss the ideas of Newton or Einstein as "pure theory". Curiously enough, those who consider Bordeu as a pure theorizer extol Brown-Séquard, who, at the famous meeting of the Société de Biologie of Paris on June 1, 1889 (one of the many birthdays described for endocrinology), largely said what Bordeu had said—but "he made an experiment". However, the experiment of Brown-Séquard was false. The saline extract of the testicle prepared with a rough technique could not contain any testicular hormone, and the result of its injection were simply due to autosuggestion. . . . No experiment, but right thinking with Bordeu, wrong experiment, but right thinking with Brown-Séquard.

All this shows that, although clinical observation and experiment are indispensable for the development of Science, the thinking, the theorizing which is behind and above observation and experiment, is much more important. It is a question of thinking right or wrong, and to think right we must follow the reasoning of the great intellects of the past. History of Medicine is important in Scientific Method.

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The edition of the *Œuvres complètes* of Bordeu, from which the passages on Internal secretion have been extracted, was published in Paris in 1815. The translation of these passages is based on the translation of Neuburger's essays.

The extracts from the *Recherches sur les maladies chroniques* of Bordeu have been made from the edition of Roussel. For avoidance of the redundant phraseology of the French eighteenth century the translation is not literal.

Section of Obstetrics and Gynæcology

President—LESLIE WILLIAMS, M.D., M.S., F.R.C.S., F.R.C.O.G.

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Behaviour of the Uterus in Early Pregnancy

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MY task is to describe and demonstrate one physical sign of early pregnancy, and at the same time draw attention to some of its implications. I will begin by a brief account of its nature.

The sign consists of an inherent muscular rhythm which—as I believe—comes into being as soon as the ovum is embedded and can be recognized clinically when the first period is due to be missed. Between the *4th and the 8th week* the rhythm becomes obvious and should not be missed by those accustomed to look for it. By the *10th week* the rhythm is changing and is a little more difficult to recognize, but it should not be missed provided the time factor is attended to. Between the *12th and 16th week* the time factor dominates the position, attendance to it becomes tedious but if it is neglected, the movement will not be recognized. By the *20th week* the cycle has become so long that its recognition as a rhythm is a matter of chance.

In brief, the action to be described and shown is an inherent muscular rhythmic cycle, easy to recognize and demonstrate up to the *10th week*, but progressively more difficult to appreciate as time goes on.

No remarks about early pregnancy would be complete without some mention of Hegar's sign, namely, that about the *8th week* the abdominal and vaginal fingers give the impression of coming into contact with each other through the walls of the decidual space.

I have found Hegar's sign disappointing and elusive, and it may be that the rhythm which I shall describe explains the inconstancy of Hegar's sign. In 1938, after one of those repeated failures to demonstrate it to a group of students, I was palpating the body of a seven weeks' pregnancy, when the uterus disappeared from between my fingers; I thought I had pushed the body to one side but could find it nowhere else in the pelvis. After a while the body reappeared in its proper position, precisely where it was before it disappeared. This confusing experience led to the search for a similar happening whenever the opportunity occurred and it was often found that the body disappeared, as it had done on the first occasion, provided one waited for what then seemed a long time.

It was evident that a movement of some sort was taking place and the idea took shape that one might learn something by using a watch to time the period of absence. In the course of time, always using a watch, it was discovered that a rhythmic movement was taking place; that a period of relaxation, lasting about 30 seconds was followed by a period of increased

tone, lasting another 30 seconds; the whole cycle taking a minute for completion before it was repeated. With increasing experience, we found that a rhythmic muscular cycle continued regularly without interruption and without noticeable change, from the *4th to the 8th week*, that is to say, during the interval between the first and second missed periods.

The beginning of this idea was stumbled upon in 1938, as a result of failure to demonstrate Hegar's sign, and the conclusion, which has taken a few minutes to describe, was reached in 1945, after seven years of trial. At that time, it was thought to be probably true. Since then, so many registrars, housemen, and students have recognized the rhythm that the probability of truth has passed into practical certainty. The rhythm has been observed in *440* cases examined during the *first twelve weeks*; *200* of these have been before the *eighth week*.

Service women, posted to gun sites, often missed one or two periods and occasionally three; almost without exception, the uterus was the typical virginal one, semi-cartilaginous in consistency and able to be flicked to and fro in the pelvis, rather like a boomerang. In the few exceptional cases which were pregnant, the uterine rhythm was obvious.

A short film was shown to demonstrate that the uterus in early pregnancy is possessed of an inherent rhythm of contraction and relaxation, the intervals of which are dependent upon the duration of the pregnancy.

The film opened with a sequence of five graphs showing the relative rhythms of contraction and relaxation occurring at 4 - 8 weeks, 10 weeks, 12 weeks, 16 weeks and 20 weeks (Figs. 1, 2, 3, 4, 5). There followed a demonstration of this movement on an excised uterus

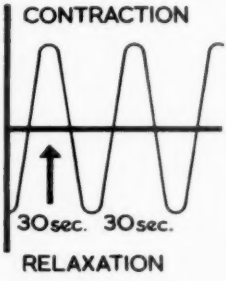


FIG. 1.

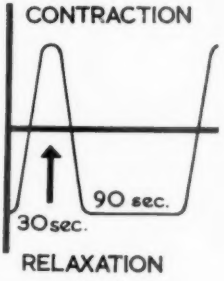


FIG. 2.

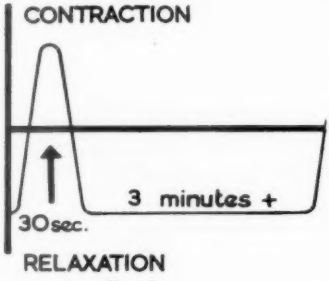


FIG. 3.

FIG. 1.—4–8 weeks. The regular cycle between the fourth and eighth week. The tonic phase of 30 seconds, followed by a relaxation phase of 30 seconds, and regularly repeated.

FIG. 2.—10 weeks. The relaxation phase now lengthened to 90 seconds, while the tonic phase is unchanged.

FIG. 3.—12 weeks. The time of relaxation is doubled, while the tonic phase is practically unchanged.

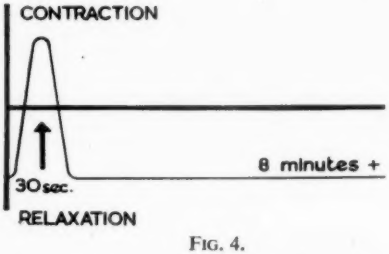


FIG. 4.

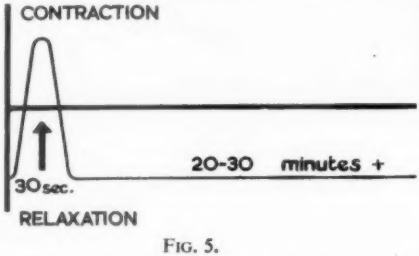


FIG. 5.

FIG. 4.—16 weeks. The time of relaxation is further lengthened to a minimum of 8 minutes, while the tonic phase remains about the same as at 8 weeks.

FIG. 5.—20 weeks. The relaxation period varies up to 30 minutes, while the tonic phase is practically unchanged.

behaving outside the body, as a uterus 6 weeks pregnant behaves inside the body. The resemblance had been brought about by artificial means.

The graphs were followed by a picture of the uterus at the height of its tonic phase. At this period, its consistency is that of a new tennis ball (Fig. 6), the fingers come in to palpate the body and it is shown to be resisting (Fig. 7); eventually it softens and the fingers sink into the body (Fig. 8). The uterus then disappears for a short time (Fig. 9), perhaps 5 or 10



FIG. 6.



FIG. 7.

FIG. 6.—The approximate size and shape of a uterus 6 weeks pregnant, at the acme of the tonic phase.

FIG. 7.—The fingers gently palpating the uterus shown in Fig. 6, its consistency being that of a new tennis ball.



FIG. 8.



FIG. 9.

FIG. 8.—The fingers sinking into the softening uterus, as relaxation begins.

FIG. 9.—The uterus, having reached the nadir of relaxation, has become impalpable for a short period, before it reappears, as in Fig. 8.

seconds, when it reappears and gradually regains its tone, pushing out the fingers as it passes towards the acme of the tonic phase. This part of the picture is intended to indicate the normal action in its proper time. The first repeat emphasizes the change and shortens the time; the second repeat is an attempt to emphasize the change still further, the time is again shortened but the uterus does not disappear.

(1) *What is the Purpose of This Movement?*

I think it is true that the placenta is not fully formed until round about the *12th week*, when in conjunction with the fœtal heart it becomes mainly responsible for the fœtal circulation. Up to this date there is no special mechanism for supplying nutriment to the ovum, unless this purpose is served by the rhythm of the uterus which regularly empties and refills a few large blood lacunæ in the walls of the uterus. After the fœtal heart and the placenta with its numerous blood sinuses have taken over the fœtal circulation, it is no longer necessary for the placental sinuses to be emptied and refilled so frequently, and therefore the rhythm changes and the resting phase becomes steadily longer as the pregnancy proceeds.

(2) *Is the Knowledge of This Uterine Cycle of Any Clinical Use?*

Those of us who are familiar with this movement regard it as being for practical purposes a certain method of diagnosing pregnancy between the *4th and the 8th week*; after the first but before the second missed period, in a woman who has not been seen before, provided she will relax her abdominal muscles and the body of the uterus will nestle comfortably between the fingers. It is desirable to have the bladder empty, and the rectum not too full. When the pelvis contains a large cervical fibroid or an ovarian cyst, it may be impossible to feel the uterus.

(3) *Is the Cycle Easy to Recognize?*

With an instructor standing by, half a dozen students in succession will assert that they have felt the change. To recognize the movement under instruction is one thing; to feel it without guidance is a different matter, for the fingers have to find out what they are expected to feel and this requires some practice. To those not familiar with the sign, I would say that without the use of a watch, allowing 30 seconds for each half of the cycle, there will be a long period of disappointment, because *5 seconds* without a watch, seem like *5 minutes*. On the other hand, with the body of the uterus comfortably resting between the fingers, and the time noted by a watch, there will be some initial failures but those who persevere will succeed.

Perhaps the most striking feature is that of a tense elastic body fading away and disappearing from between the fingers.

It matters little whether the patient is in the dorsal position or the Sims' position. With the patient on her back and the legs in the sole to sole position, it is easy to bring the tactile eminence of the vaginal finger into contact with the under-surface of the body; whereas, with the patient on her side, the tip or side of the tip of the vaginal finger must be used. In our experience one method is as good as the other. Some women relax the abdominal muscles better when on the left side, others when on the back. Every now and then it is useful to try both positions.

The cycle as described is the standard conduct between the *4th and 8th week*, but some slight variation in time should be allowed to uterine individuality.

The effect of anæsthesia.—A few cases have been examined at six weeks. It was found that the cycle continues under anæsthetic but the resting phase is prolonged from 30 seconds to a minute and a half or more.

Threatened miscarriage.—The rhythm continues unchanged as it does in incomplete abortion.

Carneous mole and ectopic.—I do not know what happens in a carneous mole [1] but would expect the rhythm to have ceased after the death of the ovum; nor do I know what happens in ectopics; the rhythm might or might not be present, but the additional pelvic lumps and traumatic inflammation, are likely to make palpation of the uterus difficult.

No suggestion is made that the recognition of painless contraction and relaxation in the pregnant uterus is anything new. It can be felt by abdominal examination at the *20th week*, if sufficient time is allowed.

Braxton Hicks was writing on this subject in 1872. He was then suggesting that the changes in uterine tone were spontaneous and not due to outside stimulus. He is reported (*see* Thoms, 1935) to have stated that the alterations in uterine tone could be observed after the *4th month*. Reference to his original article (1872) shows that he mentions the *3rd month*. He says: "After many years' constant observation, I have ascertained it to be a fact that the uterus possesses the power and habit of spontaneously contracting and relaxing from a very early period of pregnancy, as early, indeed, as it is possible to recognize the difference of consistence—that is, from about the third month.

"Up to the end of the second month the walls are still dense, but after this time the fundus will begin to be elastic, and variation in its consistence is recognizable as the end of the third month is approached."

[1] Since this paper was written, Mr. Harford Rees has told me that the rhythm fades away and disappears in carneous mole.

It is, I think, stated in the latest edition of Eden and Holland (1948) that the movement cannot be felt much before the *16th week*.

Herman stated in 1913, that Braxton Hicks was the first to point out that contractions are regular and rhythmical during pregnancy. Those before him had observed them as the result of stimulating the uterus.

Herman says: "They can be felt as soon as the uterus is big enough for the difference in consistence to be felt by the abdominal hand. To feel them, lay the hand on the uterus without friction or more pressure than that necessary for full contact with the uterine body. If relaxed at first, the uterus will be felt to become firm; if at first it is firm, it will be felt to become flaccid. Keep the hand on the uterus from 5–20 minutes. The interval between the contractions, is seldom as long as 20 minutes, they generally occur every 5–10 minutes. As the contractions pass off the uterus may become so soft that its outline can scarcely be made out at all and in a hasty examination, the presence of a pregnant uterus may not be noticed."

Professor Munro Kerr (1939) mentions occasional contractions or hardening of the uterine walls, appreciated by the educated touch from the 12th week.

It is, however, a fact, that a rhythm exists and can be recognized as soon as the first period is missed.

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Observations on the Origin of the Lower Uterine Segment in Pregnancy

By Professor F. J. BROWNE

THERE are three main views on the origin of the lower uterine segment in pregnancy:

(1) That it is the isthmus of the uterus that has been expanded or opened up, and taken up between the second and third months of pregnancy, to form part of the ovum chamber.

The isthmus, first described by the anatomist Aschoff of Freiburg, 1906, is that part of the cervix lying between the anatomical internal os above and the histological internal os below. Its average length is 4·5 mm. (Stieve), that is, about a quarter of an inch. Though forming part of the cervix its endometrium resembles that of the corpus in that the glands are simple tubular. It differs from the corpus, however, in that its endometrium does not respond well to the action of the sex hormones; it is not shed to any great extent at menstruation and the glands contain little or no glycogen (Frankl). There is little or no decidua formed in pregnancy. The glands of the isthmus also differ from those of the cervix in that they contain no mucus. Stieve has shown that after the second month the isthmus is opened up and expanded so as to become part of the corpus. This coincides with the time when the ovum completely fills the ovum chamber. When it is completed the histological internal os has become the internal os of the uterus and remains so till term. The anatomical internal os according to this view now lies at the level of the retraction ring of Barbour, that is at the junction of the upper and lower uterine segments.

This view of the origin of the lower segment has received almost universal support. Thus it is accepted by Stieve (1927), Stander, Oscar Frankl and by Munro Kerr and Chassar Moir. Barbour (1907-8) called it an "ingenious hypothesis" but did not accept it.

That the isthmus of Aschoff forms at least part of the lower segment, I have been convinced by the following observation. On 14.9.49 I did an abdominal hysterotomy for therapeutic reasons on a patient 71 days (10 weeks, 1 day) after the first day of the last menstrual period. The periods had previously been regular, type 3–4/24. A lower segment operation was done and a transverse incision through the muscle was made about half-inch below the upper level of firm attachment of peritoneum. On inserting the forefinger, which would in a uterus at term have been in the cavity of the uterus, I found that my finger was below the internal os. The internal os was partly dilated and easily admitted the forefinger which was passed

up to the fundus. The ovum was found in the left cornu and was removed. The decidua capsularis had not yet fused with decidua parietalis (Fig. 1).

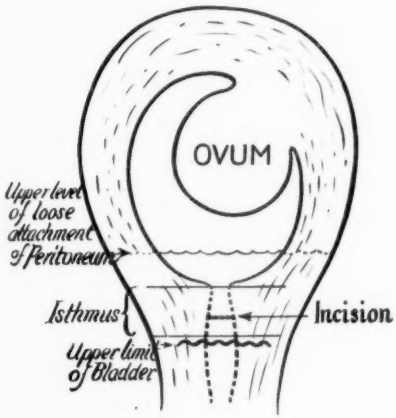


FIG. 1.

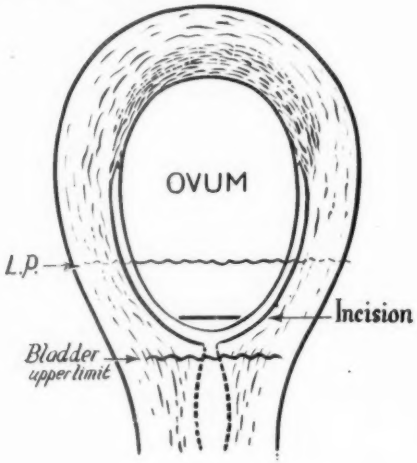


FIG. 2.

This suggests that the lower uterine segment is at least partly formed from the isthmus and that it had not yet (at 71 days) been opened up and taken up into the corpus. That the process had begun, however, is suggested by the finding that the internal os was partly dilated.

Another observation was made on 9.11.49. Abdominal hysterotomy (lower segment operation) was done at 78 days (11 weeks, 1 day) after first day of last menstrual period. The incision into the uterus was made 1 inch below the line of firm attachment of peritoneum. The finger entered the cavity of the uterus as in a lower segment cæsarean section at term. The ovum now filled the uterine cavity entirely, down to the internal os (Fig. 2).

This suggests that between the 71st and the 78th day the ovum had grown sufficiently to fill the uterine cavity and that to supply extra accommodation for it the isthmus had been opened out so as to form part of the ovum chamber.

(2) The second view is that the lower segment is formed from the lower part of the corpus only, the cervix not contributing any part of it. This view was held by Barbour and Von Franqué, who therefore believed that there was a lower segment, not only in the pregnant but also in the non-pregnant uterus. Its upper limit was the firm attachment of peritoneum on the front of the uterus which v. Franqué pointed out was 9 to 12 mm. above the internal os. Because of the observation recorded above I do not think that this view is correct.

(3) The third possible view is that the lower segment is formed both from the isthmus and from the lower part of the corpus, the part, that is, corresponding to the area of loose attachment of peritoneum. Here let me call attention to one or two anatomical points. The relation of the bladder to the supravaginal cervix is very variable, but, so far as I have been able to observe, it never reaches higher than the histological internal os. It, therefore, does not cover the isthmus. This is, of course, what we would expect if the isthmus is to form part of the lower uterine segment which has to expand passively during labour. The peritoneum is, therefore, reflected off the upper surface of the bladder at the level of the histological internal os or even below that level. As it passes up over the front of the uterus it is separated from the muscle by a layer of loose connective tissue which extends upwards above the anatomical internal os for about a half-inch. The peritoneum, therefore, covering the isthmus and this lower half-inch of the corpus is loosely attached.

I believe this third view to be the correct one for the following reasons:

(*a*) I cannot believe that the isthmus which in the non-pregnant uterus measures 4·5 mm. could ever expand sufficiently to form the entire lower segment which at term reaches to 4 in. (100 mm.) above the internal os. To do so it would have to expand about 16 times, whereas the whole uterus only enlarges to about 4 to 6 times its original size.

(*b*) If the lower part of the corpus does not form part of the lower segment there would not seem to be any purpose in its being covered by loose peritoneum. Wherever in the pelvis an organ is covered by loose peritoneum, that is wherever the peritoneum is separated from the muscle by loose connective tissue, the purpose seems to be to allow for the rapid distension of that organ, e.g. the bladder and the rectum.

(*c*) Constriction rings form in the uterus chiefly in the lower segment, above the internal os. They do not form at the level of the retraction ring of Barbour as they might be expected to do if the anatomical internal os, at which a constriction ring would be most likely to form, were at the level of the retraction ring, as it would be if the lower segment had been formed entirely from the isthmus. If, however, the lower segment comes from both the isthmus and the lower half-inch of corpus the anatomical internal os would lie somewhere about the middle of the lower segment.

SUMMARY

Evidence is brought forward to show that the lower uterine segment in pregnancy is formed partly from the isthmus of the uterus, partly from the lower half-inch of the corpus, that is the part corresponding to the area of loose attachment of peritoneum.

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Professor W. C. W. Nixon described a case which might support Professor Browne's ideas on the lower uterine segment. Recently he terminated a pregnancy of 24 weeks by vaginal hysterotomy using von Friesen's technique. Above the internal os a ring was felt which made extraction difficult since it interfered with the manœuvre of internal version. It was possible that the ring marked the junction of the lower and upper segment.

The Rarer Causes of Abdominal Pain in Pregnancy

By GORDON LENNON, Ch.M., M.R.C.O.G.

Nuffield Department of Obstetrics and Gynæcology, University of Oxford

MY interest in this subject was stimulated by a case of acute salpingitis occurring at the 4th month of pregnancy. Now, on page 458 (6th Edition) of "Ante-natal and Post-natal Care" (Browne, 1946), it is stated that salpingitis does not occur during pregnancy. These are the facts of the case:

Case history.—Mrs. G. P., aged 32, para 4, was admitted to the Radcliffe Infirmary on August 14, 1948, complaining of severe abdominal pain of three hours' duration. When out shopping she had suddenly developed sharp pain in the right side. The pain had spread out over the lower abdomen about one hour after its onset and was aggravated by movement. The patient had felt sick but had not vomited. Menstruation had been regular till April 14, 1948, since when there had been amenorrhœa. The only other significant point in the history was that, at the age of 20, there had been a history of "inflammation of the left ovary".

The woman was obese, looked distressed and in pain. Temperature was 98·8° F. and pulse-rate 108. There was marked tenderness and rigidity over the lower abdomen, particularly in the right iliac fossa. The enlarged uterus was palpated with difficulty and thought to correspond in size to the duration of amenorrhœa. There was no "shoulder-tip" pain. Vaginal examination revealed a closed cervix with no evidence of bleeding. Tenderness was elicited in the right lateral and posterior fornices. The urine showed no abnormal constituent. A diagnosis of acute appendicitis complicating pregnancy was made and immediate operation decided upon.

At operation frank pus was found free in the peritoneal cavity. The uterus was enlarged to the size of a sixteen weeks' pregnancy. The appendix was normal. No Meckel's diverticulum was found. The left tube showed old-standing hydrosalpinx and was buried with the ovary in the broad ligament. The right tube was deeply congested and pus dripped from its fimbrial end. This pus gave a pure growth of *B. coli*. Sulphamezathine and penicillin were started post-operatively. Ten hours later the patient aborted, the products of conception being passed intact. Convalescence was entirely satisfactory.

Discussion

Cases have been recorded by Fruhinsholz, Hamant and Mosinger (1929), Devraigne and Ravina (1937), Bidoire (1939), Brindeau (1939), and Metzger (1939). Their cases occurred about the second month of pregnancy, sometimes earlier, and were almost invariably diagnosed as ectopic pregnancy or acute appendicitis. Many had, in addition, chronic salpingo-oophoritis, and *B. coli* and staphylococci were obtained. Bidoire mentions that there was no great rise of temperature in his case. DeLee (1938) states, "Sometimes a pus tube forms after conception has occurred, the woman having been infected and impregnated at the same time." I have been unable to find a record of any case where gonococci were found on culture.

To ascertain if there was also intra-uterine infection I had sections made of the membranes of the ovum passed. This clearly shows focal infiltration by inflammatory cells (Fig. 1).

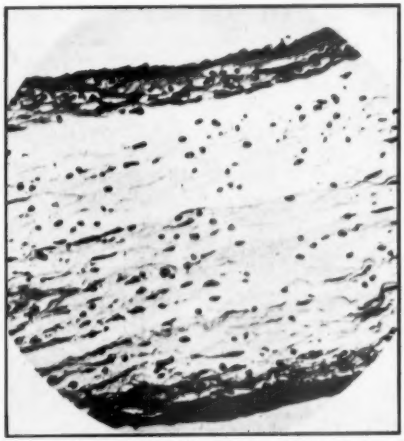


Fig. 1.—Inflammation of fœtal membranes from case of abortion with acute salpingitis. (High power.)

A similar piece of membrane was examined from another case of abortion of comparable duration but where there was no co-existing salpingitis. The absence of inflammatory cells is evident in Fig. 2. Dr. A. H. T. Robb-Smith (Department of Pathology) assures me that

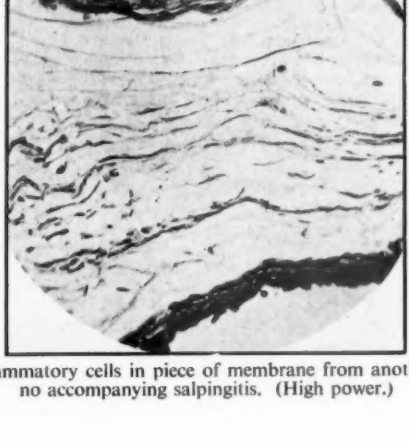


Fig. 2.—Absence of inflammatory cells in piece of membrane from another case of abortion with no accompanying salpingitis. (High power.)

it is not uncommon to find evidence of inflammation of the membranes, particularly in cases where the fœtus is macerated. In this case the fœtus was quite fresh. A pathologist will be more likely to see cases of incomplete abortion where infection is present than cases of abortion where the ovum has been expelled intact.

It is only possible to speculate as to the route of infection. Was there flare-up, due to the pregnancy, of an old focus? In favour of this was the presence of adnexal disease on the left side. The history of left "ovarian inflammation" at the age of 20 indicated some pathological condition before two of the pregnancies; why, then, had infection not flared up during the succeeding pregnancies and before this pregnancy? At the fourth month of pregnancy any space in the uterus between membranes and uterine wall must be merely potential and likely to exclude direct spread from outside. Yet the membranes showed inflammatory cells. Was this spread from the salpingitis? The possibility of criminal intervention was entertained but was denied. There remain the channels of lymph or blood vascular spread.

Mild salpingitis may account for some cases of pain in the early weeks of pregnancy for which no adequate explanation is ever forthcoming. This would suggest that the condition is commoner than is supposed. But any pre-existing salpingitis must not be of such a degree as to prevent the passage of the fertilized ovum into the uterus.

This woman could not have been expected to make the good recovery she did had her illness occurred in the years before chemotherapy. I saw her again a fortnight ago and she was 5 months pregnant, a tribute to the almost complete resolution in her previously inflamed tube. On this occasion she has had a nagging lower abdominal pain worst at the 3rd month, but never incapacitating.

Browne (1946) and also Blakeley (1933) assert that 80–85% of women complain of definite abdominal pain at some time during pregnancy. Excluding the signs of an intra-abdominal catastrophe, the pain is dismissed as being due to pulling on the round ligaments, previous obstetric trauma, orthopædic strain, &c. It is said that the mortality of acute appendicitis in pregnancy is due to delay. Better to be alive with an abdominal scar than dead without one.

Angular pregnancy as distinct from interstitial pregnancy: I find quite often when examining a patient early in pregnancy that one lateral half of the uterus is thicker, or more evident, than the other (Piskaček's sign). The woman often has quite severe unilateral pain—right-sided—and even threatened miscarriage. Indeed, she may miscarry and then the diagnosis is not in doubt whereas previously there may have been worry about the presence of ectopic pregnancy, twisted cyst or fibroid and pregnancy. I believe this condition of angular nidation to be quite common. Munro Kerr (1949) and Fahmy (1944) have stressed it and drawn attention to the difficulty in such cases of manual removal of the placenta in the third stage of labour. Some degree of angular implantation might well be the determining factor in the Duncan method of delivery of the placenta, as opposed to the Schultze mechanism when the placenta is in the fundus. It would be a question of degree of angular implantation as to whether the placenta slides out or whether part gets nipped in a cornual contraction ring—the latter state being quite a common finding at manual removal in Flying Squad cases (Joyce and Lennon, 1948).

Does stretching of scar tissue cause abdominal pain? Recently I had a woman at the 33rd week of her first pregnancy, who complained of sudden severe abdominal pain localized to the umbilicus and around it. This case was further complicated by the fact that her retroverted uterus had been perforated by a uterine sound a few years before during dilatation for dysmenorrhœa. She stated that the pain felt as though something was tearing. There was no toxæmia and no suggestion of accidental hæmorrhage. The severity of the pain and the marked tenderness caused me to perform laparotomy. The exploration was entirely negative. But the pain was better next morning, despite the abdominal incision. If coughing can precipitate hæmatoma of the rectus abdominis muscle, and even fracture of a rib during pregnancy, is it too much to suppose that the fibrous tissue of the umbilicus may be torn by effort in the later months when it is already stretched?

Lastly, I would consider constipation as a cause of *severe* abdominal pain in pregnancy. A few weeks ago I saw a woman about 5 months pregnant who complained of severe, colicky lower abdominal pain. There was a history of constipation, and certainly there were "rocks" in the colon. Temperature was 101°F. The urine was clear. Her pulse rose to 100, and results to enemata were unsatisfactory. I refrained from chemotherapy. Perhaps the fact that her appendix had been removed eighteen years before saved her from laparotomy! Eventually with movement of the bowel the condition cleared up quickly. She has since remained well.

Those who are interested in the wider aspect of abdominal pain in pregnancy will find the greatest help from a perusal of the Honyman Gillespie Lecture of 1944 by E. Chalmers Fahmy, and as a basis for discussion I reproduce the causes as divided by him into three trimesters:

First Trimester	*Second Trimester*	*Third Trimester*
Iliac fossa pain	Hydatidiform mole	Hæmatoma of rectus abdominis
Round ligament pain	Acute hydramnios	Costal margin pain
Previous obstetric trauma	Pyelitis	Concealed accidental hæmorrhage
Ectopic gestation	Ureteral spasm	Rupture of uterus
Retroflexion of gravid uterus	Appendicitis	Rupture of vein on uterine wall
Ovarian hæmorrhage	Fibroid tumour	Torsion of gravid uterus
Angular pregnancy	Ovarian tumour	Epigastric pain
	Adhesions	Gall-bladder pain
	Intestinal pain	Pain of orthopædic origin

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Section of Orthopædics

President—NORMAN CAPENER, F.R.C.S.

[*October* 4, 1949]

"Slipped" Lower Femoral Epiphysis in a Case of Eunuchoid Gigantism.—E. T. BAILEY, F.R.C.S.

The patient was a man of 29 who first attended for orthopædic advice in March 1949, complaining of pain and swelling in the right knee which was constantly giving way.

Previous history.—Examined medically at the age of 19, when non-descent of testicles, failure of voice to break and lack of body hair were observed. One year later he joined the Army. Sustained a fall on the ice, 1941, and strained his right knee which subsequently continued to give rise to symptoms. Diagnosed as displaced cartilage and eventually boarded out of the Army with this record and a diagnosis also of hyperplasia of anterior pituitary gland. Since discharge he has undertaken various occupations and has had recurrent pain and swelling of the right knee.

Examination.—Examination showed local tenderness with slight give on pressure over lower right femoral epiphysis. X-ray showed no actual displacement, but well-marked epiphyseal line of all long bones. Testes undescended. Voice unbroken. Comparatively hairless. Mental state adolescent. General poor muscle tone and laxity of ligaments, with hyperextension of joints. No other relevant findings.

X-ray of skull (Fig. 1) showed normal pituitary fossa, but marked hyperpneumatization of sinuses. Long bones showed well-marked persisting epiphyseal lines (Fig. 2), also the vertebræ. Head and tuberosities of humerus united to shaft and epiphyses of metacarpals and phalanges uniting (Fig. 3).



FIG. 1.—Hyperpneumatization of sinuses. Pituitary fossa normal.



FIG. 2.—Persistent epiphyseal line of lower end of femur and upper end of tibia.



FIG. 3.—Epiphyses of phalanges fused. Metacarpal heads commencing to fuse.

Treatment.—Treated by immobilization in gaiter plaster for five weeks, followed by muscle re-education. Symptoms relieved.

General endocrine treatment given, consisting of implantation of 1,000 mg. of testosterone into the abdominal wall in April 1949 with a repeat dose of 400 mg. in September 1949. The effect of the implantation was rapid with breaking of the voice within three weeks, increase in weight and rapid muscular development, hair developed on face, axillæ and pubis. Erections commenced to occur with nocturnal emissions.

Biochemical tests.—(*a*) 22.4.49 (1 week after testosterone implantation): Serum calcium 13·1 mg./100 ml. Serum alkaline phosphatase 15 units.

(*b*) 25.4.49: Urinary calcium excretion—twenty-four hours 2·45 grammes.

(*c*) 20.5.49: Serum calcium 10·5 mg./100 ml. Serum phosphorus 5 mg./100 ml. Serum alkaline phosphatase 10 units.

Was subsequently discharged and commenced work on a farm, but, after a few weeks, while climbing a haystack, fell with injury to knee. No damage to the epiphysis resulted and condition of traumatic synovitis resolved quickly with appropriate treatment.

Mr. J. G. Bonnin: A similar case with less well-marked gigantism is under my care. Attention was first drawn to him in a fracture clinic where he proved to have a classical separation of the lower left radial epiphysis, including a wedge of diaphysis, but only slightly displaced. His age was 39. Enquiry elicited the fact that he had never shaved. His scrotum is empty, he has little pubic hair, and his bones are light and of feminine build. His voice is a little contralto, and he has the pleasant manner of the eunuchoid, completely lacking in aggression. He is quite satisfied with his present condition, and though he was persuaded to try testosterone, has been rather disgusted with the results, and is not anxious to continue. It is thus unlikely that we shall be able to observe the effects of testosterone in hastening the union of the epiphyses.

Tumour of Humerus. (Revised Diagnosis, Case Previously Shown on March 2, 1948. Not published.)—W. D. COLTART, F.R.C.S.

Miss E. D., aged 27.

History.—On 29.8.47 fell and injured her right elbow. X-ray showed a fracture through what appeared to be an osteoclastoma of the lower end of the humerus (Fig. 1A and 1B).



FIG. 1A.



FIG. 1B

FIGS. 1A AND 1B.—X-rays showing fracture through what appears to be an osteoclastoma.

14.9.47: Biopsy of the tumour: Histological report by Professor G. Hadfield and Dr. G. J. Cunningham—"In spite of the presence of a number of osteoclastic giant cells the histological appearances do not conform with those of osteoclastoma, but rather suggest a reticulo-sarcoma as the most likely diagnosis" (Fig. 2).

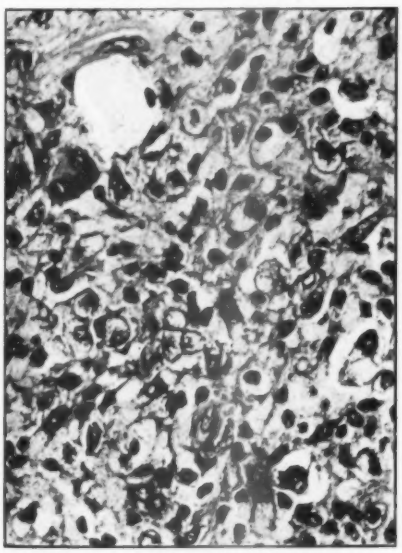


FIG. 2.—× 400. Section after biopsy 14.9.47.

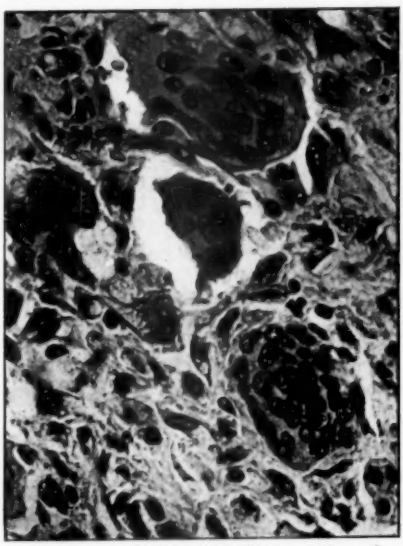


FIG. 3.—× 400. Section after resection of tumour on 15.3.48.

She was given a full course of X-ray therapy. Radiograph on 29.1.48 showed further destruction and a further pathological fracture.

On 2.3.48 the case was shown to this Section as a case of *reticulo-sarcoma*.

15.3.48: Local resection of the tumour: Histological report by Professor Hadfield and Dr. G. J. Cunningham—"Now that we have had an opportunity of examining the whole of the tumour its structure has become obvious. It is a malignant osteoclastoma and shows well-marked infiltration of the surrounding muscle. There is actual destruction of bone by tumour tissue which is not producing bone, but which has a typical osteoclastomatous structure" (Fig. 3).

She has regained good use of the elbow and so far there is no evidence of a recurrence of the tumour.

Osteochondromatosis of the Shoulder.—JOHN ADDISON, F.R.C.S., for J. S. BATCHELOR, F.R.C.S.

D. K., male, aged 31. Bookbinder.

History.—Six years ago had gradual onset of a dull aching pain around the right shoulder with no history of trauma or infection. This pain has persisted, with some remissions, and is worse after work and during cold weather. The shoulder has gradually become more stiff, and has occasional attacks of locking associated with sharp pain. He is left-handed and his disability is moderate.

Physical signs.—There is a little muscle wasting, but no point of tenderness. Crepitus is felt on movements—all of which are limited by 15° to 30°. X-ray (Fig. 1) shows



FIG. 1.—Radiograph.



FIG. 2.—Arthrogram.

multiple loose bodies, particularly in the inferior part of the joint, in the subscapular bursa and in the synovial extension around the long head of biceps. An arthrogram (Fig. 2) demonstrates uneven filling of this sheath and shows its unusual length.

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Sir Thomas Fairbank said of the cases of osteochondromatosis he had seen there were two perhaps worthy of mention. One was a middle-aged woman with a hip-joint affected. The loose bodies consisted entirely of cartilage, with no calcification or ossification, and they were faceted like gall-stones. They were packed so tightly in the joint that the neck of the femur was indented by them and appeared to be cystic in the radiograph. Some of the bodies had to be dug out of pits in the femur. The number actually collected was 163. As usual in these cases there were no arthritic changes. The other case was a colonel, one of whose ankles had been swollen for twenty years. He complained of difficulty in putting on a top-boot. On separating out the masses of loose bodies, which were of the usual type, over 60 were counted.

Tarsomégalie.—R. H. METCALFE, F.R.C.S.

Photographs of X-rays of an ankle of a boy of 10 years of age were shown. These revealed multiple loose bodies, gross overgrowth of the internal malleolus, and premature fusion of the epiphyseal line of the lower end of the tibia. Mr. Metcalfe suggested that this was probably a case of osteochondromatosis, but Sir Thomas Fairbank pointed out that the case was a very rare condition of which only one case had been previously reported in the literature under the title of "tarsomégalie" (Mouchet, A., and Belot, J., 1926, *Journal de Radiologie et d'Électrologie*, **10,** 289). He further mentioned that Mr. David Trevor was publishing a series of eight cases (*Journal of Bone and Joint Surgery*, February 1950) showing similar changes in various parts of the lower limbs and was suggesting a new and more comprehensive title.

Chronic Osteitis of a Lumbar Vertebra (Shown for Diagnosis).—R. C. F. CATTERALL, F.R.C.S.

A. A., male, aged 41. A meter-reader.

History.—Had a fall in 1944 and sustained a fracture of the transverse processes of the lumbar vertebræ for which he wore a plaster jacket for several weeks. Following this accident his back was never comfortable and in May 1947 he sought further advice. He has since obtained relief by wearing a brace.

On examination.—General health good. There is slight limitation of movement in all directions by pain. No local tenderness. No referred pain. Blood chemistry within normal limits. X-ray appearance shows increased density of the second lumbar vertebra as the only abnormality (Figs. 1 and 2).



FIG. 1.—A.P. view of second lumbar vertebra. The bone shows a uniform increase of density, with exaggeration of the internal architecture. The shape of the vertebra is normal, and the adjacent disc spaces are not affected.



FIG. 2.—Lateral view confirms both the bone change and the absence of any arthritic changes.

Mr. J. S. Batchelor: I have a patient, a middle-aged woman, who is complaining of backache, the X-rays of whose spine show sclerosis of the second lumbar vertebra. In addition, she has changes typical of Paget's disease in the lower end of the femur.

I feel that the sclerosis of the lumbar vertebra in Mr. Catterall's case is almost certainly due to Paget's disease.

Subsequent discussion considered and rejected the possibility of malignant disease and angioma as diagnoses, nor was further support forthcoming in favour of Paget's disease.

In summing up, the **President** quoted a similar case of his own which he had called "non-specific osteitis" and had treated with a bone graft.

Curettage of Tuberculous Vertebral Disease in the Treatment of Spinal Caries.—M. C. WILKINSON, M.B.

Impressed with the improvement that may follow costo-transversectomy in the treatment of vertebral caries with paraplegia, both in the patient's general condition and in the vertebral bodies at the site of operation, I have tried to apply a similar method to the treatment of tuberculous disease of the spine without paraplegia. The importance of the abscess in producing persistent disease has been emphasized by Swett *et al.*, 1940. Especially is this so in the dorsal region, an area for which the prognosis is worse than in other regions (Wilkinson, 1949). At operation the abscess is opened by removing the vertebral portions of one or two ribs, including the rib heads; the abscess is evacuated and any loose sequestra or osseo-caseous material are curetted away with a spoon; curettage should be in a forward direction away from the theca. The most important risk is that of tuberculous meningitis, due probably to direct spread to the brain through the perivertebral plexus of veins (Batson, 1940). The administration of streptomycin before operation and afterwards for at least a month should diminish this risk. Especial caution is required in applying this operation to children, owing to the increased risk of tuberculous meningitis.

Two results in adults are reported; streptomycin was only available in small quantities at the time their operations were performed.

CASE I.—W. B., male, aged 45 years. Admitted on April 1, 1946, suffering from tuberculosis of the eighth and ninth dorsal vertebræ and treated for a year in a plaster bed. Nearly a year after discharge he developed fresh girdle pains. Fig. 1 shows unsound ankylosis between the remains of D8 and 9 with surrounding caseo-necrotic material. After two months' constitutional treatment, costo-transversectomy of the tenth rib and transverse process was performed, but there was difficulty in opening the abscess. The rib was minced and inserted into a gutter made in the spines. A month later, in July 1948, costo-transversectomy of the ninth rib and process was performed; a calcified abscess and the lesion in the vertebræ were curetted. The wound healed without sinus formation. The patient was up in a brace four months after operation and returned to work eight months after operation. Fig. 2 shows the spine eleven months after operation. There is bony ankylosis between the remnants of D8, 9; the surrounding osseo-caseous material has been removed.

In February 1949 some progressive caries in D7 was noted, requiring readmission.

CASE II.—V. S., male, aged 30 years. [X-rays only shown at meeting.] This patient had been treated for slowly progressive disease of the tenth and eleventh dorsal vertebræ since 1944. He was in a plaster bed for eighteen months, but was readmitted in 1948 with a very large perispinal abscess, increase in the caries, and poor general condition. Fig. 3 shows caries of D10, 11, 12 with multiple vacuolated areas; the large perispinal abscess was only visible in the A.P. view. Costo-transversectomy of the eleventh rib and process was performed in July 1948, a considerable quantity of fluid pus was evacuated and the eleventh vertebral body was partially curetted. The rib was minced and inserted into a gutter in the vertebral spines. The patient was discharged after four months. He gained 2 st. in weight and returned to full work.

A slight sinus has persisted. Fig. 4 shows the recalcification and re-ossification in D11 due to breaking down by curettage of fibro-caseous barriers, revascularization and re-ossification. Improvement in D10 and D12 is also seen. The A.P. view showed disappearance of the abscess.

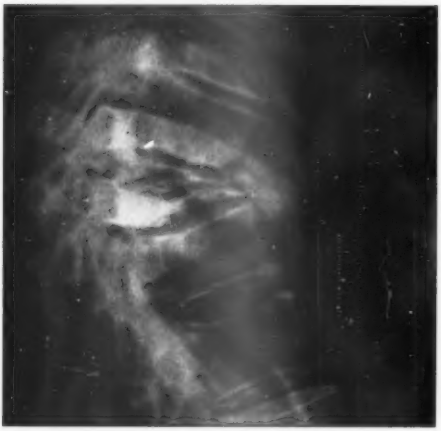


FIG. 1.—W. B. (10.4.48). Chronic caries of D8, 9 after a year's treatment in a plaster bed and a year ambulant in a brace.



FIG. 2.—W. B. (3.6.49). D8, 9 showing bony ankylosis eleven months after curettage of lesion. Patient on full work.



FIG. 3.—V. S. (4.6.48). Chronic caries of D10, 11, 12 of four years' duration.



FIG. 4.—V. S. (12.5.49). Appearance eleven months after drainage of large perispinal abscess and curettage of D11. Patient on full work.

Improvement following operation, but not cure, is all that is claimed for these two patients.

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Recurrent Dislocation of the Left Patella Medially.—W. E. TUCKER, M.B.E., F.R.C.S.

E. P., female, aged 13½.

Present history.—At age 11, early 1946, while sitting, left knee dislocated with acute pain. It reduced unaided, and no pain resulted. Repeated inward dislocations started two to three months afterwards and reduction was easily performed.

In January 1949, left patella dislocated more frequently and became painful and more difficult to reduce. Occurred when walking, standing, sitting and turning in bed.

In June 1949, loss of sensation in all left toes following "pins and needles" in leg and foot. Reduction now had to be aided.

There is no history of a definite injury, and dislocation is always to the inner side. Patella now dislocates two to three times daily at times.

On examination (21.9.49).—The left knee was slightly puffy. Movements were full; slight creaking on movement, but no sign of an internal derangement. No undue laxity of the knee, and the quadriceps were normal. The legs were straight.

The radiograms taken showed no bony abnormality.

This case was shown for opinion as to the correct treatment.

Mr. A. S. B. Bankart said that in the past recurrent dislocation of the patella had been attributed to abnormal laxity of the quadriceps, and attempts had been made to treat it by shortening the quadriceps tendon. In this case there was obvious wasting of the quadriceps, and this should be treated first. Should operation become necessary, a fascial sling from the patella to the outer femoral condyle, as described by Gallie, would appear to be the most suitable.

A Polythene Substitute for the Upper Two-thirds of the Shaft of the Femur.—H. J. SEDDON, D.M., F.R.C.S., and JOHN T. SCALES, M.R.C.S.

(This case was reported in *Lancet*, 1949 (ii), 795.)

Section of Radiology

President—S. COCHRANE SHANKS, M.D., F.R.C.P., F.F.R.

[*October* 21, 1949]

Problems in the X-ray Diagnosis of Cancer of the Stomach

PRESIDENT'S ADDRESS

By S. COCHRANE SHANKS, M.D., F.R.C.P., F.F.R.

I HAVE chosen as my subject for this Address a problem which constantly engages the anxious attention of every radiologist—that of the *X-ray diagnosis of early cancer of the stomach.* In a case of cancer of the stomach there occurs, on an average, an interval of three months between the onset of a patient's symptoms and his first visit to his family doctor. There is a further interval of three months—and this is truly deplorable—between the first visit to his doctor and full clinical and radiological investigation in hospital. When you add to these six months the earlier months during which the cancer was present but caused no symptoms, it is clear why we so often find at the first X-ray examination cancer in a developed or advanced stage. If that is true, one might ask where is the problem, since the patient does not come to us in the early stage.

But some cases do come to us early, and these we must strive painstakingly to detect.

In a cancer of the stomach certain features may give rise to difficulty in radiological diagnosis, as in the case of:

(*a*) A very small lesion.
(*b*) An unusual type of lesion, such as a plaque.
(*c*) A site that is difficult to examine completely.
(*d*) Pre-existing deformity of the stomach, such as hiatus hernia, or cascade stomach.
(*e*) Lesions of the pyloric region.
(*f*) The ulcer-cancer problem.

(*a*) *The very small lesion.*—This is the type so anxiously searched for, and so rarely found. Obviously, a growth at its inception may be too small to be seen, but this is not why one is hardly ever found in an X-ray department. At that stage they are symptomless. Even in malignant degeneration of a peptic ulcer the cancer element gives no evidence of its existence at first. I have already mentioned the time lag between onset of symptoms and examination. How helpless we are therefore to entice the early symptomless cancer into our departments for examination. Russell Morgan in the U.S.A. has launched a scheme for mass miniature barium meal radiology of the population over 40 years of age. Already he has picked up a certain number of unsuspected early gastric cancers. But is this a practical scheme? To be a really efficient sieve, the examination should be repeated every six months, which would need an immense organization, if applied to the whole population over 40 years of age. There comes a point in the national economy when further social benefits cannot be afforded, and in this Country we are over that point already.

But to return to the small lesion, as a rule the chance of detecting this is in direct ratio to the ease with which the mucosal pattern is studied, and I have no hesitation in stating my view that in the investigation of the stomach itself the technique of the complete filling by the barium meal has had its day. Berg's aphorism "The less you give, the more you see" is undoubtedly true if one is searching for a small cancer of the stomach. Fig. 1 is a case in point. This small irregularity in the greater curve was noted and discounted by a very expert radiologist. Looking at the film I agreed. It was, however, an early cancer, and a detailed mucosal pattern study might have revealed the truth. The next case (Fig. 2) showed a slight irregularity of the lesser curve. This was reported as malignant, but operation was refused. Ten months later a gross lesion was evident on X-ray examination.

(*b*) *The unusual type of lesion.*—An instance of this is the carcinomatous plaque, which may produce an appearance indistinguishable from a localized hypertrophic gastritis. Often it is simply not possible to differentiate between the two. The X-ray feature is a localized patch of coarse irregular gastric rugæ. A diffused coarse pattern involving the whole stomach is unlikely to be a growth. In such case search closely for further commonest cause of this mucosal reaction, a peptic ulcer. If no ulcer is forthcoming, reluctantly dub the condition hypertrophic gastritis, and ask for gastroscopic confirmation. In any case of the slightest doubt beg the clinician not to accept your verdict without repeated critical examination. Fig. 3 illustrates a case in point, that of a highly strung, highly efficient, hard-working, hard-drinking, business man of 45, whose stomach I have X-rayed at intervals for five years. Note the appearance in 1944; the filling defect of the pyloric antrum and the antral ulcer, both suggesting a neoplasm. Against this was the coarse pattern in the fundus, and the simple nature of the lesion is shown by an unchanged appearance five years later. Schindler states that hypertrophic gastritis cannot be diagnosed with certainty by X-rays. Many cannot, it is true, but others, including this case, do give definite X-ray signs. Fig. 4 is of another case in which the mucosal pattern suggested a carcinomatous plaque. Gastroscopy (which should always be carried out if the patient can be persuaded to swallow a gastroscope) showed a hypertrophic gastritis which has improved under medical treatment. It will inevitably relapse, and the patient will haunt the O.P. and X-ray clinics till someone takes her stomach out. The reverse picture is illustrated by the next case (Fig. 5). There was a short history of dyspepsia in this man of 62. The X-ray shows a coarse mucosal pattern and a small ulcer niche high up on the greater curve. The surgeon did a transthoracic gastrectomy, and the lesion was proved by biopsy to be malignant. And Fig. 6 shows another in which the carcinomatous plaque high up on the anterior wall was detected only after painstaking search. Fortunately, the search was stimulated by a classic history of recent anorexia, loss of weight, and epigastric pain. Again, in the next case the first picture, in 1942, shows what looks like a healed L.C.U., but with interrupted rugæ (Fig. 7). Malignancy was suggested in the X-ray report, but operation was refused, and in 1946 the patient died of starvation from a stenosing growth (Fig. 8). Note that this patient lived for four years after her cancer was first diagnosed. Had she had her stomach out at the outset and then lived four years the surgeon would reasonably have taken credit for prolonging her life.

(*c*) *The site difficult to examine.*—In this group I give pride of place to the cardia and fundus. It is a region inaccessible to radioscopic palpation and an exhaustive study of the mucosal pattern is often not possible. Add to that normal irregularity of the mucosal pattern, compared with the ordered symmetry of that of the lesser curve, and the difficulty is obvious. The cardia and surrounding fundus are blind spots to the gastroscope, and so an important corroboration may be lacking. Time was when missing a cancer in this region wasn't all that important. The patient was doomed, anyway. Now, with transthoracic œsophago-gastrectomy a satisfactory

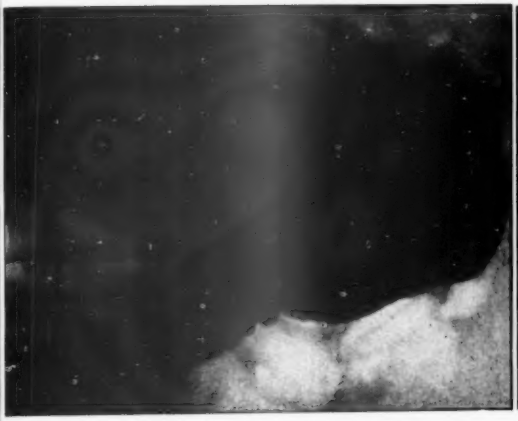


FIG. 1.—Early carcinoma of the stomach verified at operation. The only sign in this picture is the irregularity of the greater curve in the pars pylorica, at first mistaken for a pressure defect from gas in the transverse colon.



FIG. 2.—Early carcinoma of the pyloric antrum, involving the lesser curve.



FIG. 3.—Hypertrophic gastritis.

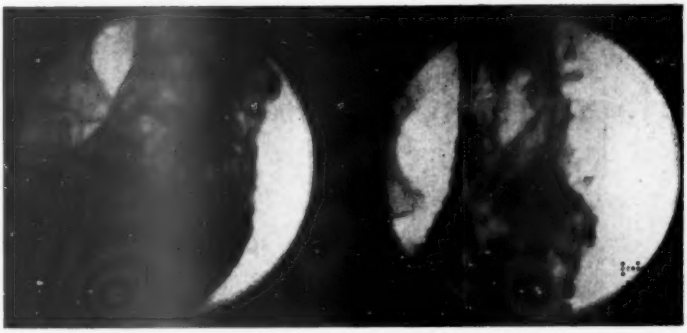


FIG. 4.—Coarse mucosal pattern suggesting a carcinomatous plaque. Gastroscopy and the subsequent history proved it to be due to hypertrophic gastritis.



FIG. 5.—Malignant ulcer high up on the greater curve.



FIG. 6.—Carcinomatous plaque high up on the greater curve.

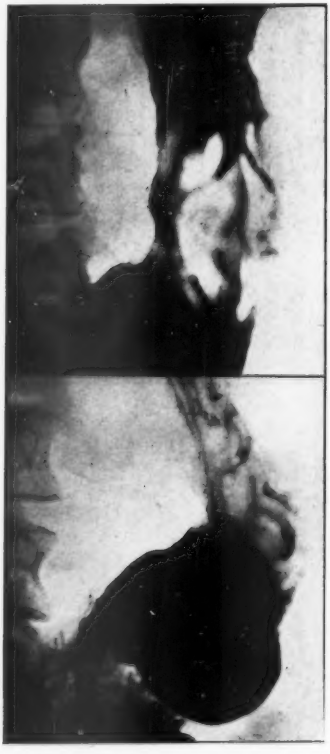


FIG. 7.—Carcinoma simulating a healed lesser curve ulcer: operation refused (*vide* Fig. 8).

operation with a reasonable mortality risk, it is supremely important to recognize growths of and near the cardia in an early stage, when surgical removal is possible.

The classic signs of established carcinoma of the cardia and surrounding fundus are well known: the delay at the cardia, with the loss of the normal intermittent spurt, the splitting of the barium stream, the coating of the tumour mass and absence



FIG. 8.—Same case as Fig. 7 four years later, showing almost complete midgastric obstruction, and reflux œsophageal dilatation.

of a regular mucosal pattern; the outlining of the tumour by the gas bubble, and by the barium in the supine view, and the thickened diaphragmatic shadow above the fundus.

In the early case few of these signs may be present, and it may be extremely difficult to differentiate between an early growth, a hypertrophic gastritis, and an anatomical variation. Rarer causes of difficulty in the differential diagnosis are indentation of the fundus by an aberrant spleen, or by an enlarged spleen in congestive cardiac failure. In one case seen by the writer fibrinous deposit in the left cupola following perforated pyloric ulcer caused a very suspicious fundal filling defect (Fig. 9).

(*d*) *Pre-existing deformity of the stomach.*—The commonest of these is marked cascade stomach, sometimes amounting to volvulus on the transverse axis. A deformity of this type may mask a lesion at the cardia, pars media, or pylorus.

Fig. 10 shows a vague irregularity in a herniated gastric fundus. This proved to be a cancer, and transthoracic œsophagogastrectomy was successfully performed. The presence of hiatus hernia may make the detection of a fundal growth extremely difficult.

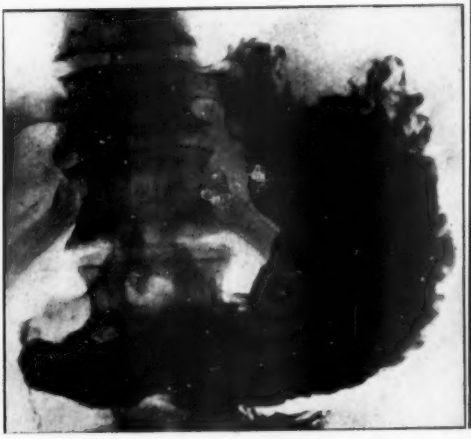


FIG. 9.—Indentation of the gastric fundus by a fibrinous deposit following perforation of a pyloric ulcer. Eight months later the fundus was normal in appearance.



FIG. 10.—Hiatus hernia and carcinoma of the fundus. Transthoracic œsophago-gastrectomy successfully performed.

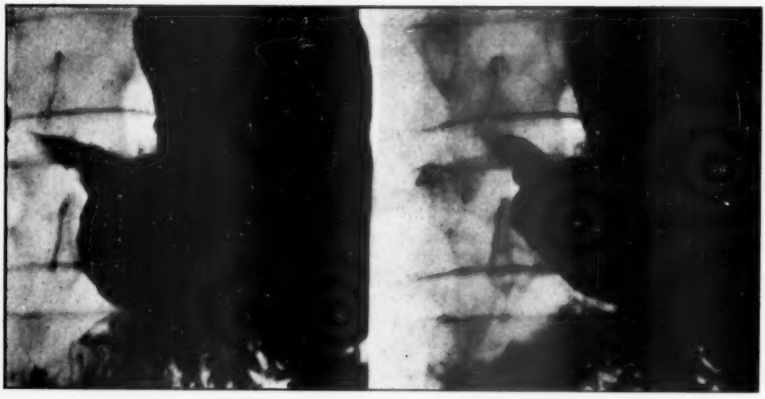


FIG. 11.—Contracted pyloric antrum following posterior gastro-jejunostomy, simulating scirrhous carcinoma.

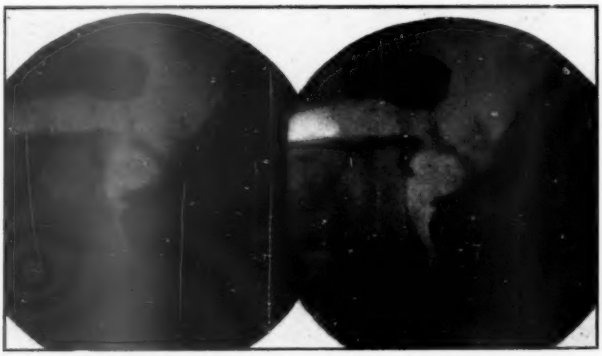


FIG. 12.—Spasm and gastritis of pyloric antrum simulating stenosing carcinoma. For details *see* text.

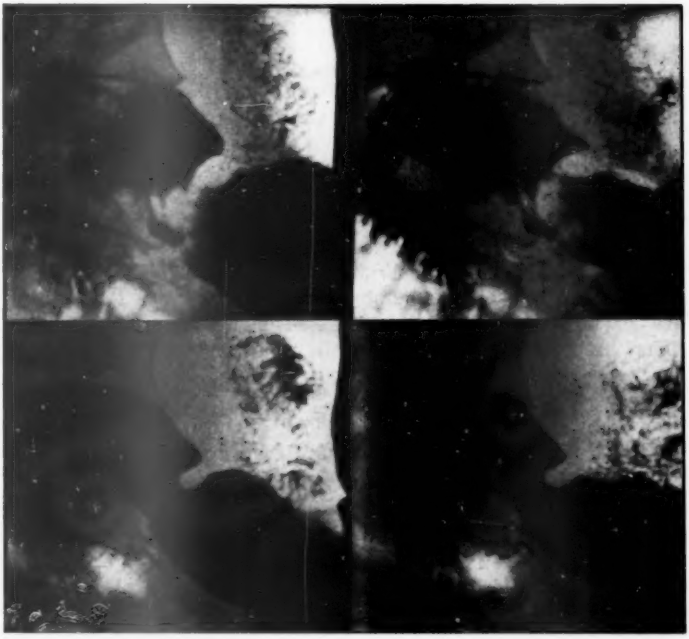


FIG. 13.—Ulcer of the greater curve, near the pylorus (upper two pictures). Its site raised the suspicion of malignancy, but the two lower pictures, taken two months later, show the ulcer completely healed.

A further difficulty arises in the pyloric region after posterior gastro-jejunostomy. The pyloric antrum may become contracted and aperistaltic, and simulate a growth, as in the case shown in Fig. 11 which had the classic syndrome—anorexia, macrocytic anæmia, and loss of weight.

(*e*) *Pyloric lesions* are notoriously difficult to disentangle. The site is a common one for hypertrophic gastritis, and an uncommon one for simple ulcer. It is a still more common one for cancer. Often radiography can show the lesion, but not its precise nature unless by serial examination over months, and gastroscopy may be of great help in doubtful cases. The case seen in Fig. 12 illustrates this difficulty. The filling defect of the pyloric antrum shows the classic appearance of a stenosing carcinoma. At operation an inoperable carcinoma was diagnosed by the surgeon, and gastro-jejunostomy performed for incipient obstruction. A year later the patient was X-rayed, and a jejunal ulcer was found, but no sign of a carcinoma of the pyloric antrum, and a year later still a partial gastrectomy was performed for duodenal and jejunal ulceration. The biopsy confirmed the simple nature of the lesion. Ulcers on the pylorus are usually suspect. So are those on the greater curve. Fig. 13 shows one on the greater curve, and near the pylorus, and yet the pictures taken after two months (below) show the ulcer to have healed later. Fig. 14 shows an almost exactly similar ulcer crater in the pyloric antrum, towards the greater curve. This case was gastroscoped, and the suspicions of malignancy confirmed. At operation there were no clinical signs of malignancy, but partial gastrectomy was performed on the radiological and gastroscopic appearances. On section a few carcinoma cells were found in the adjacent muscle coat, and in an excised lymph node.

(*f*) *The ulcer-cancer problem.*—A carcinomatous ulcer can arise in two ways: (i) ulceration of a carcinomatous nodule or plaque, and (ii) malignant degeneration of a simple peptic ulcer. Much controversy has raged around the frequency of the latter.

C. H. Mayo, Wilson and MacCarty (1924) of the Mayo Clinic propounded the view that many cancers supervened on simple peptic ulcer. This view is supported by Moynihan, Sherren, Pauchet and Maingot. Ogilvie and Schindler hold the contrary. The last mentioned states that in the long series of simple gastric ulcers he had gastroscoped serially over years, he has never met one that became malignant.

The weight of pathological evidence is against the theory. Although the pathologists at the Mayo Clinic stated that 68% of apparently simple ulcers showed microscopical evidence of cancer, such authorities as Ewing, Dible, Spilsbury, Cameron and Newcomb have placed a different interpretation on the histological appearances. As Spilsbury put it: "There are commonly found at the edge of the ulcer gland cells which have penetrated deeply into the scar tissue and are cut off from the regenerating glands. They may exhibit an atypical glandular arrangement, or may form narrow columns of cells: isolated cells are also seen. It is these cells detached from the regenerating epithelium and buried in the fibrous tissue of the ulcer which are sometimes referred to as precancerous, and which, from their position and irregular arrangement, are regarded by others as indicating malignant transformation of the ulcer". Newcomb's criteria for the pre-existence of a simple peptic ulcer in an ulcerating carcinoma are as follows: (1) Complete destruction of an area of muscle corresponding to the floor of the ulcer; (2) the presence of a large area of dense fibrous and granulation tissue in the floor; (3) the presence of endarteritis obliterans in the surrounding vessels; (4) fusion of the muscularis mucosæ with the muscular coat at the margin of the ulcer. Of these by far the most valuable is the last, and it is the only certain evidence that a cancer has arisen from a previous simple ulcer. Using this criterion, Newcomb found that only 13% of cancers showed evidence of an antecedent peptic ulcer, and that 3–7% of ulcers showed a malignant change. Matthew Stewart's figures (Table I) are of interest in this connexion.

FIG. 14.—Malignant ulcer of greater curve near the pylorus. For details *see* text.

FIG. 15A. FIG. 15B.

FIG. 15.—(A) Large simple ulcer, which healed in three months. (B) Large malignant ulcer penetrating liver and pancreas. Confirmed by operation and biopsy.



FIG. 17.—Pouching of the posterior wall in an otherwise normal stomach, simulating a large ulcer (*see* text).

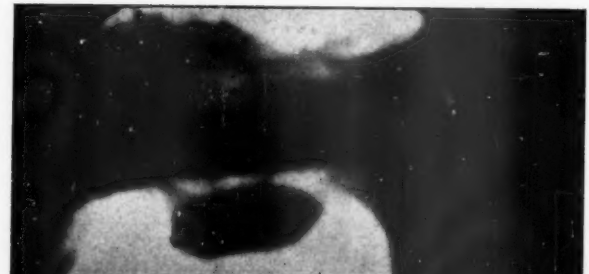


FIG. 16A. FIG. 16B.

FIG. 16.—The meniscus sign in (A) malignant and (B) simple ulcer of the lesser curve.

TABLE I.—ANALYSIS OF 733 STOMACHS SURGICALLY EXCISED FOR CHRONIC GASTRIC ULCER OR CANCER, 1921–1940 (MATTHEW STEWART)

Independent chronic gastric ulcer	459*
Independent cancer	230*
Ulcer-cancer	51
Incidence of Ulcer-Cancer	
Total stomachs with chronic ulcer	510
Ulcer-cancer 51 (10%)	
Total stomachs with cancer	281
Ulcer-cancer 51 (18%)	

*In 7 instances, unrelated ulcer and cancer were present in the same stomach.

Certain clinical evidence is also against the peptic ulcer cancer sequence being a common one. The average history of symptoms in peptic ulcer is about five to seven years; in cancer it is about six months. If the majority of cancers supervened on simple ulcer one would have expected a longer history in the cancer groups. Again, the great majority of simple gastric ulcers are on the lesser curve, while the pyloric antrum is the site of election for a cancer.

It seems, therefore, that the theory of frequent degeneration of a simple ulcer into a cancer should be abandoned. That it does occur, as in chronic ulcers elsewhere, is undoubted, but most authorities believe that not more than 6% of chronic ulcers become malignant, and that not more than 10–15% of gastric cancers arise from chronic ulcers. Curiously, it never seems to occur in duodenal ulcer, a much more chronic type.

Carcinomatous ulcer.—To determine whether a gastric ulcer is simple or malignant may be one of the most difficult of radiological problems. Often it is impossible to say from the X-ray features alone.

If ulceration occurs in an already existing tumour mass of some size, the signs of the mass itself will make the diagnosis clear, and it is in the cases of malignant degeneration of simple peptic ulcer, or ulceration of a small tumour, that the chief difficulty arises.

In making a differential diagnosis, the following points should be considered:

Size.—Any ulcer larger than 2·5 cm. in diameter should be suspected as malignant until it has been proved to be simple. The larger the ulcer the greater should be the suspicion. Many large ulcers will, in fact, turn out to be simple, but the maxim is none the less a sound one.

Fig. 15A shows a large one that was simple, and Fig. 15B one that was malignant.

Shape.—The simple ulcer tends to be hemispherical, regular in contour and sharply defined. Malignant ulcers tend to be irregular.

Meniscus sign.—Kirklin has drawn attention to an appearance, named by him the meniscus, seen in many malignant ulcers on and near the lesser curve. It is a translucent zone a few mm. in width, separating the barium-filled crater from the main barium mass in the stomach, and is due to the hard-growing malignant edge of the ulcer. Some chronic simple ulcers show the same appearance, if they have a very raised œdematous edge. Fig. 16A shows a meniscus sign in a malignant ulcer, and Fig. 16B an almost identical appearance in a simple ulcer. Some say that the malignant meniscus is intra-luminal, while the meniscus of simple ulcer is on the contour line. This is by no means invariable. A simple ulcer on the posterior wall close to the lesser curve may produce an intra-luminal meniscus.

Site.—This is of importance. Simple ulcer is usually on the lesser curve, distant from the pylorus. A malignant ulcer is variable in site, but most commonly on the lesser curve near the pylorus. Those on the greater curve—they are uncommon—are nearly always malignant.

Therapeutic test.—This is of great value in differentiating the two types. A simple ulcer should heal in a few weeks under medical treatment, a malignant one will not. Again there is a reservation. A malignant ulcer may also, for a time, get smaller during treatment for peptic ulcer. Hellmer records four such cases. He ascribes the

diminution to resolution of mucosal œdema, scirrhous contracture, and/or filling of the crater by tumour tissue. The serial X-ray examinations should therefore continue till the ulcer has disappeared and for some weeks after, to make sure that it does not reappear.

Rugæ.—In simple chronic ulcer these tend to converge to the crater. In malignant ulcer they are said to be interrupted without converging. This again is not always the case. In simple long-standing chronic ulcer which has undergone malignant degeneration the rugæ may converge to the crater, as a result of scarring.

If, after careful survey of all the above X-ray features, there is doubt (and there often is), the radiologist should not hesitate to say so. The anamnesis, the clinical features and gastroscopy will all afford further evidence, and as a last resort surgical exploration may be necessary. It is far better to cure a simple ulcer by partial gastrectomy than to miss a carcinoma.

Fig. 17 is of a case X-rayed by a colleague, who showed the case to me. We both agreed that there was undoubtedly a very large posterior wall ulcer present. It looked a cast-iron certainty, and its size and the lack of complaint of dyspeptic symptoms by the patient, a neurotic middle-aged woman, pointed to malignancy. Yet on laparotomy by an extremely competent and careful surgeon, nothing whatsoever was found—an entirely normal stomach. What caused this extraordinary pouching of the gastric wall is a mystery to me and all concerned.

What conclusions would I suggest from these observations? Firstly, that radiology is the simplest and easiest method of showing an organic lesion in the stomach, and should have first place after clinical examination in the investigation of a suspected gastric carcinoma. In the majority of cases, alas, the diagnosis is all too clear, for the majority of cases are not investigated till the disease is advanced. In many of the early cases, however, radiology can show the lesion, but not its nature. And in these cases, I would make a strong plea for the routine use of gastroscopy. Were the gastroscope easier to swallow than the barium meal, I think it should take first place in the investigation of all gastric cases. If all these methods, clinical, radiological and gastroscopic, fail to give the answer, surgical exploration is the last resort, and biopsy will reveal the mistakes of all.

Finally, may I make one comment on Ogilvie's recent and erudite article on the early diagnosis of cancer of the stomach, in which he says that we should accept the negative warnings of a penny weighing machine in preference to the positive assurance of the ten guinea Harley Street expert. Surely it must be very rare for the combined activities of the clinician, radiologist and gastroscopist to fail to find any lesion of the œsophagus or stomach in such a case. If they do fail they are not entitled to the appellation of a specialist of Harley or any other street.

While I am convinced that the X-ray method remains the most important method of examination in the investigation of gastric cases, it is, nevertheless, only one weapon, and by itself liable, in some cases, to mislead. The final decision must remain with the clinician, who in his gastric clinic must have available all ancillary methods at his disposal, radiology, gastroscopy, clinical pathology and the weighing machine, if he is to be successful in dealing with this most difficult problem, the detection of early cancer of the stomach.

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Section of Neurology

President—JULIAN TAYLOR, C.B.E., M.S., F.R.C.S., F.R.A.C.S.

[*October* 6, 1949]

Intracranial Suppuration

PRESIDENT'S ADDRESS

By JULIAN TAYLOR, C.B.E., M.S., F.R.C.S., F.R.A.C.S.

I SET about choosing my subject by trying to decide what section of neurological surgery seemed to have made most noteworthy advances during the war period. Not that I consider wars as characteristically productive of progress, indeed the opposite is more generally true, and much has to be unlearned with the advent of what is called peace. But the lot that I drew in our country's service was an unheroic one (as a prisoner in Malaya), a mole's task that withdrew me from all contact with world progress, arrived though I was at the time of life when a surgeon should survey with detachment and discrimination the march of surgical advance. Released at length from, shall we say, an obligatory search for the Way of Nirvana, and not having seen any of the rapid evolution of chemotherapy and the antibiotics, I was at once amazed at the claims for success that were now made in the management of acute cerebral abscess by chemotherapy. After some deliberation, therefore, I have chosen the subject of Intracranial Suppuration for this Address. The term connotes a large number of sites and of varieties—only a few of which I shall discuss.

Almost since the advent of antiseptic surgery we have known of varieties of abscess, for example some of the otitic ones, that are amenable to treatment by drainage; we have had some good results with sinus phlebitis, and, with the passage of years, we have come to an understanding of the management of certain cases of suppurative meningitis (1941, *Proc. R. Soc. Med.*, **34**, 447).

The subject of Acute Abscess of the Brain, formerly unspeakable unless by a few bold spirits like King of New York, is now a congenial one with the pleasant supporting sense of the confidence of accomplishment, and this blessing we owe entirely to Sir Alexander Fleming and his associates.

I shall discuss briefly some of the varieties of suppuration.

SUPPURATIVE MENINGITIS

Meningitis of otitic origin.—It was known long before the introduction of modern chemotherapy that many cases of otitic meningitis were amenable to treatment of the causative inflammation of the middle ear, a good example being acute extradural abscess complicating mastoiditis and associated with meningitis. If the extradural abscess were drained one had a good chance of clearing up the meningitis. It used to be stated that if there were organisms recoverable from the cerebrospinal fluid, the prognosis was bad, but otherwise good though the fluid might be turbid with pus. This was only the roughest of guides and had many exceptions. Indeed, it was at that time noted in the post-mortem room that when otitic meningitis was there displayed, there could commonly be found no gross and obvious bony destruction that led from the ear to the meninges. A route of infection was demonstrated by Logan Turner, using serial sections of the temporal bone, to be that of a phlebitis of the small communicating veins. Our early conception of the cause of mortality was that of an essential poverty of resistance by the meninges, and we are to some extent confirmed in this view when we realize that where we have a process of disease like that of extradural abscess, there exists an anatomical barrier that may hold up its passage and provide some delay while resistance may be organized on the meningeal side. Where, however, the extension uses the route of small veins passing right across the arachnoid space such a delay may not occur. The former may well be thought to promote arachnoid adhesions early, in the latter their formation may be too late. Now we know that an important part of the defences of the meninges is the process of localization by the formation of arachnoidal adhesions. But at once we must face the problem presented by the almost universal practice and sporadic success, of repeated lumbar puncture, a procedure that must of necessity disseminate the infection that the body, using adhesions, is apparently trying to confine.

This, I think, is a fair statement of the confusion of our ideas about the time when we began to receive the benefits of chemotherapy.

Put broadly, however, we did know that in some patients the meninges seemed to possess a vigorous power of resistance and on the whole those patients whose resistance seemed to

be most efficient, were those who had chronic mastoid disease followed by acute exacerbation with meningitis. This is exactly the kind of evidence that led Trotter to state that the tissues of the mouth and pharynx develop their own local resistance to the infections that infest these cavities, a conception that has since then been verified I believe by bacteriological means. Meningitis, however, is a diseased state in which maximal clinical effects are referable to the arachnoid and to the tissues neighbouring on it, but it cannot be considered as a pathological entity without also taking into account the simultaneous affection of the brain. To the possibility of the elaboration of local resistance I shall return later in connexion with abscess of the brain. Before leaving meningitis I should like to refer to one striking character. It is the protracted duration, the slow tempo, the lingering death, with few signs of toxæmia until the last stages, that we so often see, or rather saw, in surgical meningitis. It seems that the body has provided a powerful resistance to the virulent organisms of the accessory sinuses, perhaps one that might be more completely efficacious elsewhere, but it also seems that in the physiological circulation of the cerebrospinal fluid there has been provided so free a dissemination of infection that the arachnoid is often not quite able to defeat it.

The treatment of suppurative meningitis is now a matter of appropriate chemotherapy, and as an identical therapy is also appropriate to abscesses of the brain, I postpone reference to its practice. Suffice it that what at one time had seemed to be a defect in the defences of the meninges is now an essential part of their armament. The defensive has now luckily taken the form of an offensive.

Infective sinus phlebitis.—In this disease again we have an infective process involving a circulating fluid, but its clinical evolution is a very different one, for it is characterized by severe intoxication, the septicæmia of dissemination. Just as occurs in meningitis, an important part of the body's resistance is to be seen in the process of coagulation, indeed it is the existence of inflammatory clot that provides the diagnostic signs, and should its production fail the true nature of the disease may remain unrecognized. In sinus phlebitis, the efficiency of the process of clotting is greater than in meningitis, and if we give it the slightest assistance, for example, by ligating a big venous trunk, but one which cannot possibly prevent all circulation back to the heart from the source of infection, we may sometimes effect an immediate cure of the septicæmia, one that gives the body the opportunity of time for the clearing up of the local infection. If blood may be said to be the best bactericide that we know, its clotting may be an equally efficient arrest of dissemination. We now turn to the pathological effects of thrombosis on the tissues draining into the sinuses.

When transverse sinus phlebitis occurs we often note the appearance of signs, for example nystagmus, that indicate cerebellar involvement, and also evidence of the existence of meningitis, further evidence of the importance of the diffusion of infection in the central nervous system by the venous system. We sometimes speak a little loosely of œdema of the brain and of meningism.

To elucidate the nature of these effects we may well examine the visible changes associated in the living with phlebitis of the cavernous sinus. This sinus receives blood from the orbital, the dural, and the cerebral veins, and constitutes "a bottle neck". But the bottle neck character of the cavernous sinus is shown by the intensity of the orbital signs when the sinus is the seat of the phlebitis, for the orbital tissues swell as do the eyelids, and the eye is displaced forwards. The conjunctiva becomes so greatly swollen that it projects from between the lids like a noisome tropical fungus, the state known as chemosis. At the same time the eye and the dilated pupil become fixed, though sight is preserved. We may perhaps be tempted to regard these occurrences as the effects of venous obstruction, but if venous obstruction has any part in their pathogenesis it is a very small one. They are the consequences of an inflammation spreading through the walls of the veins large and small, and are thus a true cellulitis. The clotting power of the blood being a rapid function precedes the bactericidal effect, and thus we have a whole venous system clotted and full of active but immobilized organisms. In the case of the cavernous sinus, the immobilizing of the infected blood is not completely efficient, for we know that in the pre-chemotherapy days, if the patient did not die of septicæmia as he might do, he would succumb to meningitis later, the infection spreading to the meninges using the venous route. The following example of this disease supports these views:—

One of my prisoners developed an acute exacerbation of chronic left mastoiditis, an extensive osteitis of the petrous bone, with a left sixth nerve palsy as part of Gradenigo's syndrome. His mastoid was treated expertly by Major Farmer of the A.A.M.C., but nevertheless the infection spread to the left cavernous sinus, and there then appeared on the left side all the orbital signs described, with high fever and rigors. But he did not die rapidly of septicæmia. Indeed, I think there must have been something unusual in the character of their resistances, for among these soldiers septicæmia, often unexplained, was not at all uncommon, and its course was apt to be unnaturally long before they died of it. This soldier began to improve generally, and the eye began to recede so satisfactorily that doubt was cast by some on the correctness of the diagnosis. In about ten days the left orbit and eyelids were of natural appearance, the eye movements almost normal, the angry look of the eye was gone,

and the conjunctiva, no longer swollen, had withdrawn itself between the lids. But soon, as usual, the other cavernous sinus became affected, and the right orbital contents displayed the same series of acute effects as had earlier the left. When this was at its height, he developed obvious meningitis confirmed by lumbar puncture, and in a few more days he died, but not before the orbital signs on the right side were showing slight signs of subsidence. Post mortem, the right cavernous sinus, that later affected, was full of infected clot, but on the left side, where, I will repeat, the orbit had exhibited all the changes characteristic of cavernous phlebitis but had re-assumed normal appearances, the cavernous sinus was an abscess, a sac of pus. It was now a complete obstruction to venous flow, yet the inflammation being now restricted to the sinus itself, the orbital contents had been normal for days. It is remarkable, by the way, that the oculomotor nerve passing through the pus-filled sinus had recovered from paralysis, though it is true that similar observations may often be made elsewhere in the body. Now it may be that modern chemotherapy has, in the civilized state, abolished sinus phlebitis, this is certainly the only example that I have seen in a good many years. But, in the future, should we meet with cavernous phlebitis, it is probable that we shall cure it both as regards septicæmia and meningitis. I am now suggesting that, keeping in mind these considerations regarding the true nature of the orbital changes, we may also look forward to a return of the orbital contents to the normal.

Abscess of the brain.—It is now time to turn our attention to the suppurations of the brain itself. The subject is well divided for clinical, and until recently for therapeutic purposes, into three main groups, the Acute, the Subacute, and the Chronic. It may also be subdivided according to site, and again according to origin, whether the consequence of local or of hæmatogenous invasion. As in the case of the meninges, there has been a conception fixed in our minds for many years that the brain as a tissue has poor resistive powers in relation to bacterial invasion. Again it is doubtful if such a belief is in accordance with facts, for the brain tissue varies greatly in behaviour among the component varieties of the sub-groups. During the past fifty years, there have been recurring waves of opinion favouring treatment by aspiration at one time, by excision at another, but rarely have neurological surgeons advocated the operative drainage that forms a part of the treatment of abscesses employed by general surgeons nearly everywhere else in the body. This is peculiar, because it seems that a measure that is necessary everywhere else is unnecessary in the brain, the lesser procedure of aspiration being, as is made certain by a study of the literature, all that has been necessary in some surgeon's hands. Something similar may be found in the history of the treatment of thoracic suppuration, the treatment of acute empyema by drainage having been for long subjected to criticism and attempts having been made to substitute aspiration. Even with the advent of sulphonamide therapy, however, the general impression was that drainage was eventually necessary, though I am unable to say what is the attitude of the thoracic specialist with the chemotherapy now available. Yet we had for many years the curious theoretical juxtaposition of the brain, a poor resister, and the lung and pleura, a better, yet the first could be treated by aspiration in the hands of some, the second needed eventual drainage according to everyone. There is another undoubted fact that we should not forget, it is that a numerically large proportion of all cerebral abscesses have been treated successfully by otologists who have commonly used some form of drainage. Study of the writings of neurological surgeons, however, suggests that though this therapy has undoubtedly been successful, it may perhaps have been unnecessary, and the minor procedure of aspiration might possibly have been adequate. A third fact of importance is that certain neurological surgeons have recommended the procedure of immediate excision of acute abscesses at early stages in their formation, and have achieved success by so doing.

If, therefore, for abscess of the brain, three different therapies have been successful, varying from aspiration of pus, the least disturbing, to early excision, the most disrupting of the natural healing processes, the only possible logical deduction is that the brain must have inherent in it the capacity of dealing effectively with suppurative infections. The undoubted difficulty that we have all experienced with abscess of the brain should therefore be a technical one, the problem to be solved being how are we effectively to give to the brain the assistance that it always seems to need. There are grave difficulties in accepting our proposition, of which perhaps the greatest is our notorious ill-success before the advent of penicillin, in dealing with metastatic abscesses following on chronic suppuration in the chest.

There is one variety of intracranial suppuration that in my experience the otorhinologist has usually been quick in referring to the neurological surgeon, it is the acute form that so often follows acute frontal sinusitis, and it is deservedly sinister by reputation. It has for long been one of our greatest difficulties, and has so often been fatal that many of us came to regard it as near to hopeless.

Acute suppurative encephalitis.—The ordinary result of the drainage to the surface by, for example, a tube, of such an acute abscess as we are considering, was a large fungus consisting of swollen brain riddled with multiple foci of suppuration. Further, when such an abscess results from frontal sinusitis, the infection seems to pass inwards over a large area

regarding no natural anatomical barrier. The frontal bone is widely infected by osteitis, the inner wall of the sinus has no appearance of having been penetrated, but the infection may then be found everywhere, in the subdural space, in the arachnoid space, and in the brain where it quite soon arrives at the ventricular system.

Here then is stated our problem of acute suppurative encephalitis and it is indeed a formidable one. Some courageous spirits, however, were not intimidated, and the solutions offered have been varied.

Leaving out for the moment the question of the coverings of the brain, the surgeon's sound reaction to a spreading acute infection is to await localization, and thus the practice of repeated aspiration until an anatomically thick and therefore palpable wall should have been formed, has had many adherents in the past.

The variation practised by Clovis Vincent was a temporary osteoplastic decompression, followed by repeated tapping, and by removal in the end of the abscess when localized. But it may well be that localization may not be sufficiently complete or rapid and that the patient may succumb during the waiting period. Nevertheless the need to secure localization of the infective process as revealed by the formation of a dense and palpable abscess wall remained for some of us the controlling factor for many years, however we might deal with the treatment of the later stages.

Another solution was that of King of New York. He temporarily rolled up the scalp, removed large areas of infected bone, and then uncapped the suppurating mass of brain tissue, opening it to the surface as an acute cerebral ulcer. He laid especial stress upon the closure of the arachnoid spaces by diathermic coagulation, i.e. by a method that infallibly killed the linings of the space at the place of closure. Using such methods, he had no fear even of intraventricular rupture of an acute abscess. A fistula into a lateral ventricle was to him a far simpler affair than was the problem presented by the pathways of the arachnoid space.

Both the skull and the brain were thus treated by the excision of a so far quite unlocalized suppurative infection, and extension in the meninges was prevented by the provision of a block in the arachnoid space consisting of charred, dead tissue. That an infection spreads disastrously on account of poverty of resistance by intracranial tissues, and that it can be arrested by such measures are to my mind incompatible beliefs. Something was wrong with our premises for there is no doubt that King was highly successful. What is to my mind shown clearly here is that what was once considered a poor resistance was not intrinsic in the brain substance. It was imposed on it by its physiological mode of nutrition and the anatomical paths of the arachnoid through which this is carried on.

I mention King's name because he was a pioneer and because I had the great privilege of seeing his work at close quarters. But I intend no discourtesy to the arduous and successful labours of many others to all of whom acknowledgment is not possible. Let us nevertheless honour these for they have insisted on saving their patients' lives undeterred by theoretical objections.

I think that we should now be able to come to certain tentative conclusions about abscess of the brain.

(1) The first is that the brain has a considerable power of resisting such infections, whatever the nature of such a resistance may be.

(2) The second is that failure to cure these patients has been due to operative measures that have not been successful in preventing dissemination in the cerebrospinal fluid space. Included in the cerebrospinal fluid space is the brain substance and the ventricular system.

(3) I add a third suggestion which is not a conclusion, it is only an opinion. It is that where we have a chronically infected bone like the petrous in otitis media and mastoid disease, the brain develops a local resistance to the infection that fits it to deal with gross penetration of the dura when it occurs, either as the result of a phlebitic process or by the necrosis of suppuration.

The solution of the problem.—The discovery of penicillin and its application to the treatment of cerebral abscess have solved the problem of its management where the causative organism is penicillin-sensitive, and the solution applies to all such forms of abscess.

Sir Alexander Fleming and Sir Hugh Cairns and his Oxford followers have given us precise information regarding the distribution of the drug and its concentration in blood and cerebrospinal fluid when administered in various ways. But I wish here to say a little about the reason for its amazing success in the central nervous sytem. We have already seen that the principal difficulty in the management of abscess of the brain is to be found in the dissemination of the infection in the cerebrospinal fluid space, but now at last we are freed from the need to attempt to prevent this. For with penicillin the less obstructed the arachnoid space, the clearer the path open for the diffusion of the drug. Further we must remember that the cerebrospinal fluid not only circulates in the arachnoid space, it also perfuses the brain substance, and it is this fact that enables penicillin to destroy infection in the brain with the completeness and certainty that characterize its action. Thus that which was a disability imposed by a nutritional method has become an essential means by which our

curative drug is diffused. It follows that our method of giving the drug must comply with the needs imposed by its path of distribution. In order that it will reach for certain every infected tissue when dealing with suppurative processes in the brain we must start our penicillin on its course as near as possible to the place where the cerebrospinal fluid begins its journey. Fortunately this is easy by the method of ventricular puncture. Systemic penicillin therapy has also a function in these diseases, it is the treatment of the focus whence the central nervous system was infected. Its indications thus vary with the nature of the primary disease.

The following cases treated by myself and my assistant, Mr. Bernard Harries, each illustrated some part of our problem:

(i) Subacute abscess of the brain.
(ii) Chronic abscess of the brain.
(iii) Abscess metastatic from chronic thoracic suppuration.
(iv) Acute suppurative meningo-encephalitis.

(i) *Subacute Abscess of the Brain*

Boy aged 9 referred to me by Dr. Blake Pritchard.

History.—Pain in the right ear two months before present illness. Fourteen days before we saw him he had fallen down in the street and subsequently had malaise with shivering, still later right frontal headache and vomiting.

On admission to University College Hospital he presented head retraction, drowsiness, nystagmus, cerebellar signs in the right arm and leg. Lumbar puncture produced clear fluid containing 132 cells per c.mm., 75% of which were polymorphonuclear, the remainder lymphocytes. The right ear-drum was reddened and there was inspissated discharge in the meatus.

Operation.—A diagnosis of right cerebellar abscess had been made by Dr. Pritchard on November 2, 1948. A burr hole was made behind the bend of the right transverse sinus and a needle put into the abscess from which a few cubic centimetres of pus were aspirated. No firm wall was felt. 20,000 units of penicillin were instilled into the abscess cavity. Both lateral ventricles were tapped and penicillin was instilled into one of them twice daily to begin with, later once daily for three weeks. Systemic penicillin was also given as treatment of the otitis media. The abscess was explored with a needle on two later occasions, and on the second, three weeks after the operation, no fluid was obtained. No organisms were ever grown from the pus.

The boy made a good recovery and is still well. This is the kind of cerebellar abscess that in the pre-chemotherapy days I should have treated by means of tube drainage, and I should have been surprised had he not recovered. The same applied to very many cases of otitic temporal abscess. A drain, however, always results in scarring of its track, and a needle is far better.

Comment.—This boy had a chronic otitis media, and when he developed cerebellar abscess the infecting organism was so greatly attenuated in virulence that it failed to grow in a medium. His cerebellum and the arachnoid which the infection had crossed undoubtedly had developed a strong resistance and perhaps it was a locally developed one. In the days of tube drainage, it was the custom of the majority of surgeons, no doubt with the doctrine of low resistive power in mind, to leave these tubes in for long periods. Such treatment must result in scarring anywhere in the body, and a scar probably matters more in the brain than elsewhere. I always doubted the need for this prolonged drainage though on occasion I have been intimidated into maintaining it for a few weeks. It is quite possible that this boy could have been adequately treated by aspiration alone, by penicillin into the abscess cavity alone, or by intraventricular penicillin alone.

(ii) *Chronic Abscess*

Girl aged 9.

History.—For nine months she had had intermittent headaches which for two months had been very severe and accompanied by vomiting. Before the headaches began she had had a pain in the ear, had been examined by an otologist who noted a reddened drum. For some time a diagnosis of otitic hydrocephalus had been accepted and the child had been treated by repeated lumbar punctures and systemic penicillin. But the disease had speedily progressed and the child had recently become so much worse that a diagnosis of cerebral tumour had been made.

On examination she was drowsy, there was a right external rectus weakness, right facial weakness, bilateral upgoing great toes, and absent abdominal reflexes. There was a high bilateral papilloedema. Ventriculography showed that the right lateral ventricle was dilated and displaced to the right. The left lateral ventricle could not be filled.

Operation.—A diagnosis of large left temporal chronic abscess was made. A burr hole was made in the lower left parietal region just behind the ear. At a depth of 4 cm. an abscess with a just palpable wall was encountered and 38 c.c. of thick yellow odourless pus were aspirated. The ventricles were again tapped the left one being now found. 100,000 units penicillin were instilled into the abscess and into the ventricle. Daily ventricular penicillin was instituted and the abscess cavity reaspirated on several occasions, penicillin being instilled. On the last occasion no pus was found, only a drop or so of clear fluid.

Five weeks after her operation ventriculography showed no abnormality and her papilloedema and other signs had disappeared. Again no organism was grown from the pus. Again a powerful resistance had been developed.

Comment.—About this child I should not have been at all confident in the pre-chemotherapy days. Drainage of a cavity 4 cm. from the surface of the posterior temporal lobe has elements in it both of inefficiency and of the danger of infected fungus. In such a position

I should not have considered excision, for it must have been followed by hemiplegia and aphasia. This child recovered rapidly and is now well, taking daily luminal. She had a chronic abscess. It has not been excised and I do not anticipate further trouble unless it be the onset of epilepsy. Had, however, this abscess been situated elsewhere in the brain, it is just the sort of one that many surgeons would deem it proper to excise, though possibly as a secondary procedure.

(iii) *Hæmatogenous Abscess Secondary to Chronic Thoracic Suppuration*

This kind of abscess has had in the past a truly evil reputation. The late Mr. Tudor Edwards told me that he had never known one recover, and so bad were the results that there were good physicians of great experience who preferred to leave these patients alone, hoping for the natural temporary subsidence of symptoms that sometimes did occur.

Here is a typical example. Among the sailors nearly but not quite drowned at the sinking of the *Prince of Wales* on December 10, 1941, was a petty officer who contracted pneumonia and then an empyema. This was drained by a surgeon, but unluckily inefficiently, because through the tenth rib, and he developed a chronic sinus. After temporary healing, about a year later he came to see me as a prisoner and in our so-called hospital we drained his cavity more suitably, later doing a small operation of the Estlander type. After this all went well until one day about a week later he said he could not see to the left. It did not disturb him as he could read, but an examination of his visual fields showed that he had a left homonymous hemianopia with preservation of the whole macula. We made a little hole in the right occipital region and encountered with a needle some white inoffensive pus in the brain at a depth of less than 1 cm. from the dura. We thought the prognosis hopeless. We put in a drainage tube. All seemed to be well until after the lapse of a few days he complained one morning that for the first time he could not read, and, as expected, we now found that the homonymous defect passed vertically through his macula. I explored his brain again and found the abscess larger. His state became steadily worse and he died. Post mortem his whole right occipital lobe was seen to be a bag of pus with no visible abscess wall other than the grey matter. The extent of the abscess could not be accurately determined because in addition to there being no lining, the brain was decomposing in the tropical climate of Singapore, but the following may be the explanation of the progress of the visual changes.

Macular representation is usually held to lie in the posterior part of the occipital cortex, exactly where I found the abscess on the day it first caused symptoms when macular vision was still unaffected. But it has been held that there is bilateral representation of the macula in the occipital cortex, and it has also been stated that the path of the contralaterally destined fibres lies in the posterior part of the corpus callosum. If this be correct anatomy, it is possible that the macula at first escaped while the abscess was still small, but when it grew to the size seen at post-mortem, it may be that the advantage of bilateral representation was lost as the result of affection of the fibres passing from the right radiation to the unaffected left occipital cortex. I refer to this patient because he exemplifies what I have noted as a major difficulty in attributing strong powers of resistance to the brain. Here was a brain in a not grossly emaciated man whose other reactions to infection seemed to be natural, which clearly opposed no defence at all to the spread of an infection, for his abscess seemed to be nothing but a spreading quiet necrosis whose macroscopic limits could not be recognized. I should not have quoted it at length, had it not had much in common with what we were accustomed to see in such cases at home before the war. Now, however, things are very different, as the following account makes certain. In March 1947 a man aged 27 was admitted to University College Hospital suffering from progressive drowsiness of one or two days' duration. He had suffered from bronchiectasis and four years earlier a lobectomy had been performed. He was semicomatose. There was right facial weakness, absent abdominal reflexes, weakness of the right arm and leg with down-going great toes, there was no papilloedema. His cerebrospinal fluid from lumbar puncture showed a pressure of 300 mm. and slight turbidity. An immediate ventriculogram showed the body of the left lateral ventricle narrowed and displaced to the right and upwards. A left parietal abscess was then aspirated, no organism being grown from the pus. Penicillin was given as in the other cases into the abscess which had no palpable wall at all and into the ventricles, and he made a progressive recovery.

A month later no further pus could be obtained. Eighteen months later he professed himself perfectly well except for a further exacerbation of his bronchiectasis.

Such a recovery was a new thing to me though I am glad to say that it is not now a solitary example.

I now turn to the last and most serious of my groups, the catastrophe of

(iv) *Acute Suppurative Meningo-encephalitis*

In my hands before the war this disease had been invariably fatal, though I believe that others have been more successful. In October 1948, however, a boy aged 13½ was admitted to the Royal Ear Hospital suffering from acute *left* frontal sinusitis and left maxillary antritis. The left antrum was irrigated and systemic penicillin was given, under the direction of Mr. Formby and Miss Wadge. After a lapse of two weeks he was better though an occasional slight evening fever was noted. His frontal headache then returned and he began to vomit, but there was no further discharge from the nose. There was neck rigidity, Kernig's sign, and a slight *left* lower facial weakness. The cerebrospinal fluid from lumbar puncture showed a pressure of 180 mm. water and was a little turbid. Later he had a rigor, became drowsy and developed a *left* extensor plantar response. The fluid was now more turbid and contained large numbers of pus cells. His state rapidly deteriorated, and two days after the onset of cerebral symptoms, Mr. Formby and I explored both his frontal sinuses. Neither contained any pus or fluid, but the mucosa was dark and œdematous. The dura was exposed on each side, no extradural abscess being found. A small exploratory cut was then made in the dura of each side. On the left side, the side on which the frontal sinusitis was known to have existed, nothing was found and the opening was closed. On the *right* side a collection of thick pus was found in the

subdural space. Its extent could not be estimated, but seemed to be wide, and the depth of the lake of pus was not more than 2 or 3 mm. This *right* subdural space was drained with a thin soft tube. Double ventricular puncture was performed. The ventricles were clearly small. On the *left* side I had a little difficulty in finding the ventricle for it seemed to be smaller than on the right. During search for the left lateral ventricle the needle was withdrawn, and a drop of pus from the brain substance in the left parietal region was aspirated. The fluid in the ventricle when it was entered was in small quantity, was viscid and turbid.

The frontal sinuses were left open, and treatment by ventricular, by lumbar, and by systemic penicillin was instituted and sulphamethazine was also given. The pus yielded a *Streptococcus viridans* on culture.

The case was regarded as probably hopeless, he lapsed from drowsiness into coma, and then needed tube feeding. After some days he began to show some signs of improvement. When he recovered consciousness he had complete aphasia for a day or so, and later began to throw right-sided Jacksonian fits. Pus had practically disappeared from his lumbar fluid. A fortnight after his operation a ventriculography was done which showed now some dilatation of the ventricles with displacement of the ventricular system to the right. A burr hole was now made in the *left* temporal region, and a large collection of subdural pus was encountered in the temporal and parietal regions and was drained. He then began to improve more rapidly, his fits ceased and he began to lose his aphasia. He remained in hospital for some months gradually improving, and being given luminal. He was discharged apparently well. In May 1949, six months after his operation, he came to hospital suffering from generalized epileptic seizures. Contrary to instructions, his luminal had not been taken after discharge. A ventriculogram was now normal, luminal was again ordered and no further fits have been seen.

Here was a patient suffering from meningitis, from subdural abscess over the right hemisphere, from swelling of the left and suppuration in its substance. Later a subdural collection over the left hemisphere also was found and drained. A clearer example of diffuse suppurative meningo-encephalitis cannot be imagined yet apart from epilepsy he has made a complete recovery. It calls for no comment save an obeisance to Sir Alexander Fleming, for no surgeon could have helped this boy without penicillin.

These few cases are selected for description as exemplifying types, from about ten successful ones, treated on these lines. I have, however, lost three. The first was a lady with acute suppurative meningo-encephalitis, who at post-mortem appeared to have succumbed to septicæmia and pneumonia, her cranial contents being apparently then clear. The second complicated a chronic empyema and he died, I think, because I succeeded in aspirating only a few cubic centimetres from a large abscess. The third had a deep-seated parietal chronic abscess, alongside the falx, with a thick wall that I did not succeed in penetrating with my needle. It burst somewhere into the cerebrospinal fluid space, and he died. Both these last two deaths were certainly associated with, and it is likely were due to, technical failure on my part.

I think it is fair to say that we have now a successful treatment for all grades of virulence and chronicity of abscess of the brain due to penicillin-sensitive organisms. I have no experience of streptomycin in these cases because it has been unnecessary and naturally one prefers the less irritating drug. Before ending I should like to say just a little about cicatrices in the brain.

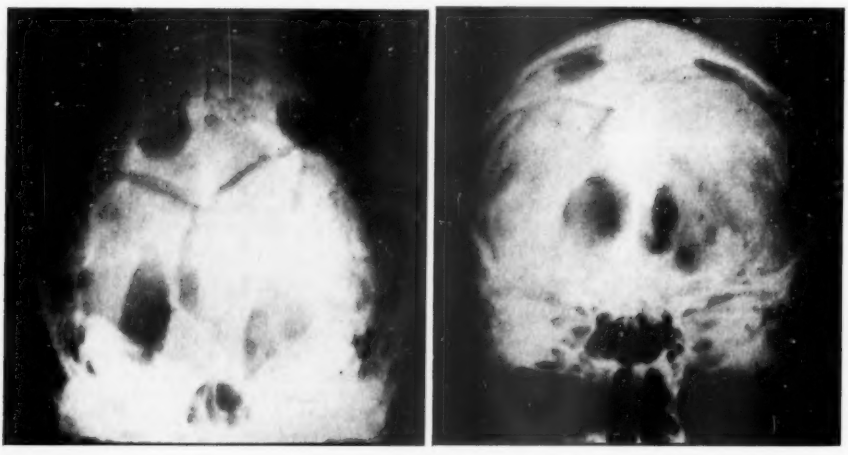
The method we employ is always distribution of penicillin in the central nervous system by repeated ventricular puncture, beginning sometimes twice daily then continuing for a space once daily. We have had no trouble with our punctures which are almost painless once the incision has been made and closed. It has been recommended that a canula should be tied into the lateral ventricle. I do not think that this can be said to be a sound procedure, for a foreign body cannot be kept *en demeure* without causing some necrosis. If we tie a catheter in the urethra for a day, we get urethritis however cleanly be our methods. If we keep a needle in a vein we get thrombosis. It is the custom nowadays quite light-heartedly to keep tubes in the œsophagus for long periods, but I have seen linear ulcers in the thoracic œsophagus many inches long in the post-mortem room following such therapy. Now we are beginning to learn that among the many patients who survive such measures, there is an increasing incidence of benign stricture of the lower œsophagus. I cannot help thinking that if we tie a canula in the brain substance we shall get a line of necrosis at its site. Recently in the case of a child suffering from hydrocephalus following the treatment of tuberculous meningitis by streptomycin, a canula was tied in a lateral ventricle contrary to my instructions, not, I hasten to say, by one of my assistants, for even now, in these days of control by registrars, I have some slight influence over their activities. A cerebrospinal fistula resulted that had to be closed by operation, and an air picture demonstrated the track that the necrosis made. We have seen nothing similar with ventricular puncture repeated once or twice daily for weeks.

I feel sure that the members of this Section will support me in the view that every scar in the brain is a danger, and the bigger the scar the greater the likelihood of its causing epilepsy. In the surgical treatment of the brain therefore a prime consideration of every surgeon should be that all scarring that is not absolutely necessary should be avoided.

This brings me to the question of excision of abscesses. I have many times excised chronic abscesses in the past, but with penicillin I am sure I shall not do so often in

the future. Yet a study of the literature of the present day cannot fail to show us that just now the wave of opinion is in favour of the excision of abscesses, almost as routine. I do not say that a cerebral abscess need never be excised, but I know for certain that excision is usually unnecessary. I think that perhaps the demonstration of loculi by the use of radio-opaque substances injected into the cavities of abscesses has something to do with the urge to excise. I should like here to point out that to inject a foreign body such as thorotrast, or an iodine oil, or any other opaque substance, into a closed abscess cavity is asking for persistence of the infection as plainly in the brain as it would be anywhere else in the body. There is no primary reason to suppose that it may be any less provocative of chronicity than is a sequestrum, or a knot of so-called absorbable catgut, in the depths of a sinus. I cannot help thinking that the widespread habit of demonstrating the existence of abscesses radiologically by this means may be a cause of the need to excise them late. Last year I was consulted by one of our nurses at University College Hospital. Some time previously she had had a frontal abscess treated by a neurological surgeon whose name is famous, for whose work I have nothing short of reverence, and whose permission I have to discuss her case. She had a small opening in her frontal bone, and she would frequently come to me with swelling of her forehead and eyelid—also the slightest headache and a flicker of raised temperature. I sent her back to the surgeon who had saved her life and he agreed that if possible we should do nothing. Eventually he excised the still active cicatrix of the abscess and she has since remained well. The interesting thing is that the site of the abscess was still shown before this last operation by a persistent opacity in the frontal lobe, the shrunken relic of such a radiological demonstration.

Abscesses of the brain may be slow in healing. Here is a pair of ventriculograms. No. I shows displacement of the ventricular system to the left after a right frontal abscess of traumatic origin had been drained and was apparently soundly healed. I thought we had another and needled the brain fruitlessly at an unnecessary operation. No. II shows what another



No. I. No. II.

FIG. 1.—Ventriculogram No. I shows displacement of the lateral ventricles to the left due to swelling of the brain substance persistent after the healing of an abscess of the right frontal lobe. No. II shows the state of the ventricles a month later.

month of leaving the brain alone did for him. The ventricles are now back in their right position. The natural slow resolution of some of its suppurative inflammation is a request from the brain that it be not irritated by the unnecessary injection of foreign substances that it cannot absorb.

Finally, who can doubt that the scarring resulting from a needle and the resolution of an abscess assisted by penicillin, is far less extensive than that produced by the gentlest of excising surgeons.

[The Address was profusely illustrated by slides. Owing to pressure on space only one figure has been inserted.]

Section of Epidemiology and State Medicine

President—W. H. BRADLEY, D.M., M.R.C.P.

[*November* 18, 1949]

The Mechanism of Antibody Production

By C. O. STALLYBRASS, M.D., D.P.H.

FEW subjects have led to more controversy than immunity. The rival theories—cellular and humoral—of Metchnikoff and Ehrlich have been fused in a general Theory of Immunity giving due place to both phagocytosis and antibody production, but the mechanism of antibody production has become almost as controversial an issue as was that of the Metchnikoff-Ehrlich debate. Many hypotheses have been advanced by Manwaring (1928), Breinl and Haurowitz (1930), Alexander (1931), Mudd (1932), Sabin (1939), Burnet (1941), Sevag (1945, 1946), and Northrop (1948), a number of which have been shown in the light of newly acquired data to be inadequate. Recent advances in relation to the biochemistry of genes, viruses, bacteria, and the granular biosomes of cells, point to the important functions performed by nucleo-proteins in vital processes, to which no place in antibody production has been given except a brief reference by Monné (1948).

E. B. Wilson said in 1899 "Nuclein" (meaning nucleo-protein) "may, in a chemical sense, be regarded as the formative centre of the cell which is directly involved in the synthesis of complex organic matters. The specific character of the cytoplasm is determined by that of the nucleus. The nucleus cannot operate without a cytoplasmic field". In antibody production there may be differences between the processes following the introduction of soluble and of particulate antigens, the latter being subject to phagocytosis, but the essential intracellular mechanism involves the interaction between nucleus and cytoplasm which Wilson's intuition foretold.

In propounding any hypothesis of antibody production certain accepted facts must be given due weight:

(1) Free antibodies are modified globulins mainly produced in the reticulo-endothelial system, principally in the cells of lymph-nodes and spleen and probably the skin, but also in the mobile phagocytes. Associated with the experimental production of antibody there is commonly a rise, which may be absolutely greater, of normal gamma globulin in the blood. The spleen and/or lymph-nodes often enlarge concurrently.

(2) The curve of rise of antibody content frequently takes an exponential form, i.e. resembles population increase curves.

(3) Bissett (1947, 1948) showed with frogs that by altering the environmental temperature in the first and second periods of antibody production two distinct and successive mechanisms were operative.

(4) A second injection, given perhaps after all detectable antibody has disappeared from the blood, produces an even more marked response, the so-called "anamnestic" response. This induced antibody-production mechanism may persist throughout life. The stimulating effect of the repeated injection bears only moderate quantitative relation to the amount injected.

(5) Particulate antigen appears to produce a more lasting response than a soluble antigen (Freeman).

(6) Antibodies are specific not only to the antigen but also to the species of animal injected (Heidelberger, 1938). There is a genically controlled specificity of the antibody which the normal globulin inherits and an induced immunological specificity, corresponding with the specificity of the antigen with which it can visibly unite. The mechanism of production of this high and twofold specificity is the crux of the question.

(7) The enzymes involved in synthesis are not self-replicatory.

(8) The same is true of antibodies. Serum globulin injected does not reproduce itself autocatalytically.

(9) Antibody is not produced in appreciable quantity in the absence of living cells.

(10) The antibody produced may far exceed in quantity that of the antigen injected; there is no direct mathematical relationship.

Examination of earlier hypotheses of antibody-production mechanism shows that many of them are vitiated by involving one or more of the following concepts which are either known to be, or probably are, fallacious:

(i) *Incorporation of fragments of the antigen in the newly forming globulin antibody.*—This seems inadequate to permit of the high specificity of the process of antibody production. Moreover as antigens may be polysaccharides, &c., such as gums, entirely foreign to the animal body, such incorporation appears to be metabolically impossible without complete degradation, again with complete loss of specificity.

(ii) *The Buchnerian hypothesis of incorporation of the whole antigen in the antibody molecule.*—This is equally untenable on the grounds just given under (i). Further, as shown by Berger and Erlenmeyer (1931) and Hooker and Boyd (1932), using arsenic-containing haptenes, the amount of antigen was much too small to permit of even a single atom of arsenic being retained in each antibody molecule so produced. This hypothesis must likewise be rejected.

(iii) The concept that the antigen is retained within the cell where its molecule impresses its configuration upon each newly forming globulin molecule. This mechanical coin-and-die comparison, whilst in accord with some facts, appears incompatible with (4) above. It often would involve the retention of the antigen, apparently unchanged, throughout life. Two forms of this hypothesis have been put forward, namely that the "impression" is made either on existing normal globulin or upon a globulin precursor which Northrop (1948) termed a "proteinogen" and Wrinch termed a "proteon". None such has been chemically demonstrated.

As Northrop himself points out (1948) the observation of Dougherty and his colleagues (1944*a*, *b*) made upon malignant lymphocytes of mice will, if confirmed, render this hypothesis likewise untenable. Dougherty transferred such lymphocytes to animals of the same species where they reproduced the disease by rapid cell division; the process was repeated by inoculating serially a new generation of mice with the malignant cells with identical result. The original mouse with malignant lymphocytosis had been injected with a specific antigen against which its lymphocytes contained antibody; the final generation of lymphocytes contained the specifically induced antibody, although the amount of original antigen transferred with each serial transmission must have been excessively small. On these grounds the concept of "moulding" the antibody, or its precursor, appears to fall to the ground.

Burnet's (1941) hypothesis is based upon the seeming similarity of the process of antibody production to that of the production of adaptive enzymes in bacteria. In both cases the presentation of a new and foreign substance, a substrate in the adaptation of enzymes, an antigen in the case of antibody production, evokes a specific alteration in the metabolism of the cell involved. The essential similarity is the modification of an existing enzymic process. Burnet regarded a lasting modification of the intracellular proteinases (kathepsins) by contact with the antigen as operative. If the antigen is contained in a particulate entity, e.g. a bacterium, this must, presumably, first undergo cytolysis, for this process to be effected. Burnet

dismisses the concept of continuing spatial contiguity of antigen and globulin in the mechanism.

Since Burnet put forward this hypothesis great developments have taken place with regard to protein synthesis and structure, to the systems of enzymes involved in carbohydrate synthesis, and to the transfer of energy from the carbohydrate oxidation-reduction cycle to phosphate-carrying co-enzymes. The reversible action of enzymes, such as proteinases, whilst theoretically possible, requires the activity at higher levels where specificity is implanted, e.g. in the formation of polysaccharides of a nucleo-protein; this has been shown, by the work of Griffiths and Avery (McCarty *et al.*, 1946) in the case of specific pneumococcal capsular polysaccharides, to be dependent upon a specific nucleic acid molecule, presumably operating, after transfer, in conjunction with the specific pneumococcal protein as a nucleo-protein molecule.

Whether proteinases can by themselves reversibly synthesize a mixture of the "building blocks", such as amino acids, amines and polypeptides, into specific proteins, is open to question. Chantrenne (1949) considers that acyl phosphates play an important part in protein synthesis. It is in this way that the energy transfers, commonly recognized as essential to synthesis, can be effected (Lipmann, 1941). The not improbable production of amino acids from keto-acids by amination forms a link between carbohydrate and protein synthesis. There are probably other routes available.

In relation to the nucleic acid moiety of nucleo-proteins the structure of some of their component nucleotides, e.g. adenylic acid, is almost identical with some of the co-enzymes, e.g. adenosin diphosphate, and is closely allied to some enzymic phosphatic groups; this relationship seems to indicate a comparable metabolic role, namely, anabolism and katabolism and the simultaneous energy transfers (*see* Schlenk, 1949). There is an accumulating body of evidence that the regularly repeating tetranucleotide structure of nucleic acids, i.e. polymerization, postulated by Levene, is an inadequate representation of the specificity of the nucleic acids, a specificity mirrored in the specific part they play, e.g. in specific pneumococcal polysaccharide synthesis. Nucleic acids were considered by Gulland (1947) to contribute as much to the specificity of the nucleo-proteins as does the protein moiety of those gigantic molecules. Indeed Boivin (1948) has expressed the opinion that every species of bacterium has its own specific nucleic acids.

The characteristic nucleic acid of chromatin (genes) is the desoxyribo-nucleic acid; treatment of cells with ribonuclease removes the corresponding acid from the field and the remaining desoxyribose acid can, by appropriate means, be shown to be a constituent, small, but probably important, of cytoplasmic structures which may be termed generically biosomes; these are divided by cytologists into mitochondria ("fibre-granules"), chromidia, &c., though the lines of division are not always clear (Ludford, 1928; Ludford *et al.*, 1948; Claude, 1941; Bourne, 1942; Brachet, 1945; Monné, 1948; &c.) The presence of ribo-nucleic acid in the cytoplasm, mainly in biosomes, though also in nuclear structures, e.g. chromosomes and nucleolus, is associated with its active proteosynthetic role.

There is, indeed, a general consensus of opinion that ribo-nucleo-protein plays an active part in protein synthesis and that the richness of ribo-nucleic acid content and the intensity of synthesis are correlated (Boivin, 1948).

The metabolic turnover of the ribo-nucleic acid both during growth and during antibody formation is very much greater than that of the desoxyribose acid (Chargaff and Vischer, 1948); Brachet (1945, 1948) from his investigations of the metabolism of developing ova finds evidence to indicate that in the sea urchin there is, within the early hours of development, a rapid conversion of ribo-nucleic acid into the desoxy-acid. How this can be done is not understood and it seems not improbable, in the light of the study of introduction into metabolism of artificial compounds containing radio-active isotopes, that it involves degradation of the lengthy molecules into their

constituent ribo-nucleotides with subsequent conversion into the equivalent desoxy-nucleotides, reconstitution of the nucleic chains, and finally polymerization or end-to-end linkage.

Studies by Harris and Harris (1949) show a parallel increase in ribo-nucleic acid and of antibodies in plasma cells of lymph nodes during immunization, by a peripheral route, but no increase in either when non-antigenic substances are injected. Both Fagraeus (1948) and Ehrich and his colleagues (1949) regard plasma cells as playing a major part in antibody production when the antigen is subcutaneously introduced.

Every hour 200 million lymphocytes enter the blood stream (Trowell, 1947) replacing an equal number which return to the reticulo-endothelial system, there to be destroyed. In Sabin's (1939) ingenious studies of production of antibodies in lymphocytes of animals injected with Heidelberger's dark-red azo-dye antigen, she observed how the dye disappeared from these phagocytes contemporaneously with the production of antibody. Further they were seen to shed a portion of their cytoplasm (exoplasm) into the blood stream; this elegant demonstration of the locale of antibody production in the lymphocytes' cytoplasm is convincing.

The fundamental concept of chemical genetics (Zechmeister and Went, 1948) is that each gene controls a single step in biosynthesis; correspondingly Keilin has shown that the effects produced by an organized system of enzymes differ from the summation of the products of each enzyme acting alone; synthesis is genically controlled and is not haphazard. The genes are efficiently protected from environmental influences by the nuclear membrane. The study of mutants of yeast (Beadle, 1948; Stephenson, 1949) has shown that the loss of a single gene, in relation to amino-acid synthesis, results in an inability to synthesize the acid.

Ludford, Smiles and Welch (1948) have photographed by phase-contrast and ultraviolet light the granules of lymphocytes (mitochondria) which contain nucleic acid which is strongly absorptive of ultraviolet light at 2650 Å, so much so that if over-exposed the light is lethal and they lose their nucleic acid envelope and then no longer reveal its presence. In dividing malignant lymphocytes, where protein synthesis is actively proceeding, these granules can be seen to distribute themselves equally into the two daughter-cells during cell division. They appear therefore to be both proteo-synthetic and self-replicating (*see also* Bourne 1942 *re* multiplication of mitochondria).

Attention has again been directed to such self-replicating cytoplasmic bodies and the manner in which genically controlled structures may receive intracytoplasmic modification from externally derived substances present in the cytoplasm. This, as already stated, is the crux of the problem of antibody production. Such "cytoplasmic inheritance", which in no way affects Mendelian inheritance through gametes, has been postulated again in more precise manner by Sonneborn (1943), Darlington (1944) and Spiegelman (1946). Potentiality for enzyme formation may segregate in Mendelian fashion; such gene-enzyme potentiality may be developed cytoplasmically. Spiegelman and Kamen (1946) find, from their experiments in cells whose enzymic metabolism has been largely inhibited by sodium nitrite, that such *self-duplicating entities in the cytoplasm are nucleo-proteins rather than the enzyme itself.* This accords with the finding that all self-duplicating units are inseparably linked with nucleic acids. By competition with other units within the cells for the building blocks of proteins and enzymes the enzymic constitution of the cell is determined. Darlington terms bodies of genic derivation and cytoplasmic location, controlling molecular activities, *plasmagenes.*

Both the ribo- and desoxyribo-nucleoproteins easily aggregate with phospholipids forming a nucleo-protein-lipid symplex. Spiegelman and Kamen (1946) consider that in adaptive enzyme formation a plasmagene Pl combines with an enzyme precursor Pr and a substrate S to form a symplex PlPrS, resembling the phospholipid symplex termed PLAPS isolated by Miles and Pirie (1939) from Brucella. From such a symplex the new enzyme is derived. This concept is supported by Monod (1944,

1945) who also postulates a common enzyme precursor of species-specific character.

It must be pointed out that the enzyme precursors best known, e.g. pepsinogen, trypsinogen, are unmasked, at any rate in the case of pepsinogen, by a loss of a part of the molecule—about one-fifth. The true intracellular proteinases (kathepsins) are activated (Fruton, 1941) by ascorbic acid or substances, e.g. glutathione, containing sulphydryl groups. The inert precursor appears to be a device to inactivate the enzyme so that it does not act katabolically to the detriment of the cell; some lipid-protein attachments appear to perform a similar function (Monné, 1948).

The occurrence of precursors of enzymes which, or some of which, are proteins—possibly globulins—armed with a prosthetic group, commonly a vitamin, is still problematical in the sense of a species-specific substance which can be moulded into a particular shape upon the presentation of a new substrate. Similar species-specific protein (in this case globulin) precursors such as Northrop's proteinogen and Wrinch's proteon, are even more problematical.

What does appear likely is that the plasmagene—presumably desoxyribo-nucleic acid—ribo-nucleic acid, and the antigen, enter into a symplex and effect the production of a *new plasmagene symplex or system*, with the appropriate enzymes, and control—within the mitochondria or other biosomes—the production of the new globulin, with or without the globulin precursor. The two-stage process demanded by Bissett is allowed for; the exponential curve of antibody production can be explained by (*a*) multiplication of mother and daughter cells containing the new system and (*b*) multiplication of the specifically modified biosomes within those cells. The anamnestic response corresponds to the re-stimulation and renewed multiplication of the appropriate cytoplasmic system, which appears to involve a large increase of ribo-nucleic acid. So stimulated, the intracellular enzymes and building blocks would be diverted largely to the building of the new globulin, but the production of normal globulin would be simultaneously stimulated and a large increase of normal globulin might ensue.

This hypothesis, which it is hoped contains the minimum number of hypothetical activities to accord with the known facts, is not simple, but neither is the normal process of protein synthesis which requires further alteration to permit of the known twofold specificity of animal antibodies; it is based (*a*) on a partial analogy with adaptive enzyme production, (*b*) on the genic activities of nucleo-proteins, and (*c*) those of enzyme systems located in (*d*) mitochondria and/or other biosomes of cytoplasmic location. It is largely a modification of previous hypotheses, notably that of Burnet. So stated it is hoped that it will escape Occam's razor "*Entia non sunt multiplicanda praeter necessitatem*".

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Professor J. R. Marrack: *Structure and Formation of Antibodies.*

We are agreed that antibodies are individual globulin molecules that have the special property of combining specifically with molecules of the homologous antigen or haptene. Before approaching the problems of the formation of antibodies we have to consider the structure of globulins and the difference between any antibody molecule and other globulin molecules that gives it the specific ability to combine with the corresponding antigen.

Globulins are proteins and are mainly composed of amino acids combined in peptide chains. The backbones of these chains are made up of the first two carbon atoms of the amino acids and the nitrogens of the NH_2 groups: the "tails" (e.g $—CH_2.CH(CH_3)_2$ in leucine, $—CH_2.CH_2.COOH$ in glutamic acid) stick out from the chain. The chains can be bent and coiled: this bending and coiling is limited, as the tails occupy space and get in each other's way. In the fibres of silk it appears that the C and N atoms of the backbone are approximately in a plane and the chain is not coiled. In the fibres which fall into the α-keratin group (hair and myosin) the chains are supposed to be arranged in a series of loops in the plane of the backbone, each loop consisting of 9 amino-acid residues. The

molecules with which we have to deal are not fibres, but are compact and have been likened variously to balls, buns, eggs and cigars; the chains in these compact molecules must be much more looped or folded than those in the fibres.

Of these compact molecules we know most about the structure of horse hæmoglobin—unfortunately one that is a poor antigen and has been little used in immunology. This according to Perutz and colleagues (Boyes-Watson, Davidson and Perutz, 1947; Perutz, 1949) has a hatbox shape (a cylinder, height 34 Å, diameter of base 57 Å). The hatbox is made of four layers just under 9 Å thick. These layers consist of peptide chains, which Perutz (1949) thinks have small loops, similar to those of the α-keratins, at right angles to the plane of each layer and bends, at longer intervals, in the plane of the layer. The tails of the amino-acid residues lie in the planes of the layers, though some of the longer tails may be bent and stick out from the base and top of the hatbox.

The 4 hæm groups lie on the side of the hatbox, at right-angles to the lengths of the chains; each occupies about 1/40 of the area of the side. The 4 histidine residues, to which the hæm is attached, must therefore lie at the 4 bends of the peptide chains—these being the only positions where the side chains could protrude in the right direction. Haurowitz (1949) considers that the hæm groups are specifically attracted to the globulin molecules by other groups besides the histidine residues. Hæmoglobin molecules, therefore, have specific combining groups at the bends of the peptide chains.

The molecules of other proteins—horse myoglobin, serum albumin, egg albumin and ribonuclease (but not insulin)—appear to be made up of layers, like those of hæmoglobin. One dimension of the molecules of most proteins, as calculated, is approximately the same as the height of the hæmoglobin cylinder. It is possible that the molecules of antibodies and of protein antigens may also be made of layers of peptide chains and that these chains may have loops and bends like those of hæmoglobin. The molecules of antibodies in rabbit and human serum and diphtheria antitoxin of horse serum are usually compared to cigars (prolate spheroids)—length 300 Å, thickness 34 Å. An elongated brick-shape would fit the data equally well. The bricks might consist of continuous layers with peptide chains running the whole length of the molecules or a row of 4 structures with shorter chains. Globulin molecules can be split into halves transversely to the long axis in the first stages of digestion by enzymes; they are not split into layers. The second suggestion therefore appears more probable.

The only forces by which an antibody with such a structure can be bound to an antigen, serum albumin or globulin for example, are (1) Van der Waals' forces, (2) Electrostatic attractions between oppositely charged groups, (3) Hydrogen bonds. These forces are, first, not specific; any two atoms are mutually attracted by Van der Waals' forces; any positive charge attracts any negative charge; hydrogen bonds can be formed between any oxygen, nitrogen or sulphur atoms. Secondly they are short-range forces. The Van der Waals' attraction varies inversely as the 7th power of the distance between two atoms. The force of attraction when the distance is 1 Å is 1/128 the attraction at 0·5 Å. Thirdly, these forces are relatively weak; if therefore only a few pairs of atoms of two molecules can be brought into close contact the attraction between them will be small; if on the other hand a large number of atoms of the two molecules can be brought into close contact the attraction between the two molecules will be strong.

The sides of the hatbox molecule of hæmoglobin and the ends and sides of the brick-shaped molecules of more elongated proteins are not smooth, as the tails of the amino-acid residues project from the surface to varying heights. The tail of a leucine residue may project by about 4 Å (which is 7% of the diameter of the cylinder) and the tail of a tryptophane residue by 6 Å. These tails differ in lateral dimensions. The width of the leucine tail is about 2 Å widening at the end to 3·6 Å; that of the tryptophane tail is about 4·5 Å. There are gaps between these projections. If the projections on the surface of an antigen molecule fit into the gaps on the surface of an antibody molecule the attraction between them will be strong. We therefore believe that the ability of an antibody to combine specifically with antigen is due to the arrangement of the amino acids on its surface in a pattern that fits the pattern of those of the antigen.

We know from work with artificial antigens that the determinant groups of the antigens may be relatively small; the formation of the combining sites of the antibody may, therefore, involve a rearrangement of the pattern of a few amino acids only; but this is not necessarily always the case.

Pauling (1940) suggested that the specific patterns of an antibody might be formed by appropriate coiling of the ends of a peptide chain, after it had been formed. The possible patterns of coiling are limited for steric reasons. I do not think that the number of possible variations of coiling could be enough to provide specific binding sites for all the possible antigens. Incidentally the two ends of a peptide chain cannot be similar, as Pauling appears to assume; there must be a free NH_2 at one end and a free COOH or CO—NH_2 at the other.

It has not been possible to detect any difference between the composition or structure of one antibody and of another, or between antibodies and non-specific globulins. But the analyses have, so far, not been so complete that they exclude such differences.

The groups by which a globulin molecule, which is an antibody, combines with an antigen are distinct from those by which it combines when it is itself an antigen. Thus diphtheria antitoxin (a horse-serum globulin) can combine with toxin when it is also combined with antibody to horse-serum globulin. I suggest that the antibody groups may be on the ends of the brick and the antigenic groups on the side.

We have, therefore, to consider how the introduction of an antigen can induce the appropriate arrangement of the growing antibody molecule. This involves some hypothesis about the synthesis of proteins. There are two theories:

(1) The *template theory* according to which the amino acids are arranged on a template in the correct pattern and then synthesized by a team of enzymes.

(2) The *conveyor belt theory* according to which the growing protein molecule is presented to a series of specific enzymes in appropriate order; these enzymes add the appropriate amino acids from an unselected collection of amino acids.

I do not think the second theory is possible. It would involve the existence of as many proteases with distinct specific activities as there are amino acids; there is no indication of the existence of all these specific enzymes.

The known structure of the hæmoglobin molecule and the theory of the specific character of antibodies emphasize the importance of arrangement in space. It is very unlikely that the peptide chains that constitute these molecules would spontaneously loop, bend and pack themselves into the structures found in the complete molecules. The theory proposed by Dr. Stallybrass seems to me to fail to account for arrangement in space. There must be some kind of template, not only to pick out and arrange appropriate amino acids in the right order in the peptide chains, but also to fold and pack the peptide chains.

According to the template theories of Breinl and Haurowitz (1930) and of Mudd (1932) an antigen is deposited in the places where serum globulins are formed; amino acids are fitted into an appropriate pattern on the antigen, just as the amino acids of the complete antibody fit to the antigen; the amino acids are then synthesized into a protein, which is the antibody. The theory of Pauling (1940) differs in that it supposes that the antigen does not influence the synthesis of peptide chains, but only determines the pattern in which their ends are coiled; it is, all the same, a theory according to which the antigen acts as a template. The recent experiments of Dickey (1949) provide an example of the induction of specific affinity by such a template action. Silica gel is formed by adding acid to a silicate solution which contains methyl orange; the methyl orange is then extracted with methyl alcohol. The gel so formed adsorbs methyl orange specifically. If butyl orange is used in place of methyl orange the gel formed adsorbs butyl orange most strongly, ethyl and propyl orange less strongly and methyl orange least.

I do not think that, so far, the theory as proposed by Mudd and by Breinl and Haurowitz differs essentially from that of Burnet (1941). The template is acting as part of the enzyme system of the immunized animal; it might be called a co-enzyme. The great difficulty, in any theory, is to account for the persistence of the formation of antibodies and of the ability to respond to a second stimulus with a rapid and large formation. A guinea-pig that has been sensitized by a protein may remain sensitive for the rest of its life. An even more remarkable example is the persistence of sensitiveness to tuberculin through several generations of subcultures of the fibroblasts of tuberculous animals (Moen and Swift, 1936). This is the fundamental objection to the theory that supposes that the antigen itself serves a template. Work with isotopes has shown that an animal's own proteins change continually; we can hardly imagine that a foreign protein would persist for long. The amount of tuberculin carried with the first inoculum of cells, in the experiments of Moen and Swift, would be reduced to an ineffective amount after two subcultures. As Burnet concludes, the factor in the enzyme system that determines the specific structure of antibodies must be reproduced in the body of the immunized animal. But it is hardly conceivable that an animal could copy a foreign group such as the *arsonic* acid, which is the determinant group of very efficient antigens.

In accordance with the theory that antibodies are formed by lymphocytes it has been maintained that γ-globulin can be extracted from lymphocytes. Kass (1945) found that a protein extracted from lymphocytes of human lymph glands would form a precipitate with antiserum to human γ-globulin. I have repeated Kass's procedure, using the large lymph glands of a patient who died of Addison's disease. The extract formed a precipitate with antiserum to γ-globulin, but also with antiserum to albumin. The concentration of γ-globulin estimated by the optimum proportions method of Dean and Webb (1926) was about 1/3 of the concentration of albumin and only 1/100 of the total protein concentration in the extract. It is probable that the γ-globulin found was derived from a small amount of serum that contaminated the lymphocytes.

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Section of Surgery

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DISCUSSION: GASTRODUODENAL HÆMORRHAGE AS A SURGICAL EMERGENCY

Dr. A. H. Douthwaite: I suppose it is in the minds of most of us at this Meeting to consider the indications for surgery when severe bleeding has occurred as the result of peptic ulceration—either gastric, duodenal or anastomotic. I shall not refer to such rarities as benign tumours of the stomach which may cause bleeding, or to carcinoma which is obviously a surgical problem. I do not, furthermore, propose to spend any time on elementary points of differential diagnosis, such as determining whether the blood does, in fact, come from the digestive tract rather than the respiratory passages. There are, however, a few conditions, always unsuitable for surgery, which may give rise to hæmorrhage and a mistaken diagnosis of peptic ulcer. I shall refer only to examples which I have met with in the course of practice during the last twenty-five years and shall not give an inclusive list of the possible diagnostic hazards.

In the first place cirrhosis of the liver may present a great difficulty in its recognition. We must always remember that many of the signs which might be elicited in a patient otherwise well will be masked in one who has bled profusely. The history of indigestion occasioned by the cirrhotic liver and associated gastritis is not always easy to differentiate from that given by a chronic ulcer, and such physical signs as enlargement of the liver and spleen, though helpful when present, cannot be relied upon to save one always from a diagnostic pitfall. When we remember that although the bleeding in cases of cirrhosis usually comes from the varices in the œsophagus, yet it may also come from an actual ulcer in the stomach superimposed on the chronic gastritis so frequently present with cirrhosis of the liver, the extreme difficulty of making a certain diagnosis will be at once apparent. In fact, no matter how careful one is, sooner or later one is almost certain to make the mistake of assuming a peptic ulcer of a chronic nature when none such exists. Even if we had time to carry out liver tests, and even if the patient were fit enough to support these, they are extremely unreliable in anyone who had bled profusely. The effect of a big hæmorrhage is also to cause a reduction in the size of the spleen which might be palpable before the hæmorrhagic incident. A less common mistake, but one of which I have seen three examples in hospital, is to diagnose peptic ulceration and hæmorrhage when the underlying disease is chronic nephritis with uræmia. In these three instances the patients were admitted with a history of recurrent abdominal discomfort for several months and no other symptoms until a profuse hæmatemesis put their lives immediately in jeopardy. Certain points should, however, prevent one from perpetuating the mistake. The patient is always abnormally drowsy for the degree of anæmia, the tongue is always dirty and covered with a brown fur, there is invariably considerable wasting with loss of subcutaneous fat and there is also well-marked thickening and tortuosity of the palpable arteries and usually enlargement of the heart. Even if urine is available it does not necessarily contain an appreciable amount of albumin. Once the condition is suspected a blood urea determination will settle the diagnosis, for these hæmorrhages never occur until the uræmia has reached a level of at least 100 mg. per 100 mil. The cause of the hæmorrhage is a widespread gastritis.

Chronic indigestion as the leading symptom in tuberculosis of the lungs is well known to all of us. Gastroscopy in such cases usually shows a pale œdematous mammillated gastric

mucosa, but it is not perhaps generally recognized that on this account acute ulceration may arise and cause profuse hæmorrhage. A careful overhaul will usually raise suspicion of this unusual event, but I have seen one example in which the patient was opened on the wrong assumption that a chronic ulcer was at the root of the trouble.

The last mistake to which I have to refer is in the case of hæmorrhage due to arterial hypertension. Fortunately this is quite uncommon, but when it does occur it may be very profuse, resembling in that way the persistent epistaxis which is a better known feature of the disease. Here the mistake should not be made because there are always signs of the secondary cardiovascular changes of hypertension and there is never any history of indigestion except perhaps the flatulence common to patients with an overstrained heart.

Severity of hæmorrhage.—It is generally agreed that all figures and opinions relating to the value of surgical or medical treatment for gastroduodenal hæmorrhage are completely useless unless they are given in relation to the severity of the hæmorrhage. Probably the only point of contention between the physician and surgeon relates to severe hæmorrhage arising from peptic ulceration. We all have our ideas of what we mean by severe, but it is difficult to get any criterion generally accepted. Although the hæmoglobin level is not an accurate guide, especially in the first few hours following the bleeding, I think we might take it that any hæmorrhage which has reduced the level to 50% may be regarded as severe. If we watch such a patient over the next few hours and find a slow fall of hæmoglobin but no further rise of pulse rate, no restlessness, no further vomiting of blood or the passage of loose red or reddish-black stools, we can be fairly sure that the hæmorrhage has been brisk but is rapidly subsiding, if it has not already stopped. With efficient medical treatment nearly all these cases will recover. In looking through various records I have collected thirty-five examples such as I have quoted, and only one died. This was a man of 65 with gross arteriosclerosis; two days after the hæmorrhage had apparently ceased he had another brisk hæmorrhage and died within two hours. Efficient medical treatment means an adequate supply of fluid, blood transfusions if the hæmoglobin is 40% or lower, and the securing of rest. Although morphine is the traditional drug to use and I believe the right one, it is a mistake to employ it alone. It causes spasm of the pyloric sphincter, it tends to induce vomiting in many people and does not always induce that peace of mind which is so essential to an alarmed patient. A quarter to half-grain of morphine should be injected together with 2 grains of papaverine hydrochloride and 3 grains of sodium phenobarbitone, the whole given intramuscularly on account of the bulk of the solution. This is far more satisfactory than morphine alone, it is reliable and in my view safe. It might be argued that the fatal case I have mentioned would have been saved by operation. This is doubtful. All surgeons are aware of the extreme difficulty of finding and securing the bleeding point when dealing with a patient with a chronic ulcer. If to play for safety we operated on all patients whose hæmoglobin was in the region of 40%, at least 95% of the operations would be entirely unnecessary and it is doubtful whether they would be free from operative mortalities. It is impossible to decide which of the patients who have bled severely will go on bleeding and which will stop. If, however, we are satisfied that the bleeding *is* continuing we then come to our real problem—the patient whose hæmoglobin is now perhaps in the region of 30% or lower and who is gravely ill. I have notes of 7 patients who at the time of admission or shortly afterwards were so ill as to be apparently moribund. They were cold, sweaty, confused, drowsy, greyish in colour, restless, with an imperceptible pulse and the blood pressure, if it could be measured at all, was below 70 mm. of mercury. Hæmoglobin levels were from 28% to 18%. 6 of these patients died directly as the result of the hæmorrhage. Blood, of course, was given by drip transfusion and it ran out yet faster from the gut. One, who was relatively young, the age being 35, evidently stopped bleeding when he appeared to be about to die, and then recovered in a miraculous fashion. What would have happened if these patients had been operated on? 6 patients in a similar condition, on whom surgery was advised, either by me or others, died, 4 on the table, 2 within an hour of getting back into bed. It is true that these cases go back over several years, and it is only perhaps in the last few years that the importance of giving a really large transfusion has been appreciated. We all agree that the obvious approach to a bleeding point is a mechanical one—that is to say surgery, but the peculiar difficulty in relation to the stomach and duodenum is that in order to get to the point the patient has to be subjected to what is an enormous strain for an exsanguinated body. Then there is the hunting for the bleeding point, the trauma of its exposure, and closure. It cannot be expected that the human body deprived of nearly all its blood could recover in these circumstances. I believe that the solution must lie in our ability to detect earlier the persistence of bleeding in patients who come in after severe hæmorrhage but who do not, as yet, exhibit the signs of collapse I have described. I am coming to believe that in a case of a patient whose hæmoglobin is below 50% and who, in spite of the sedation which I have mentioned, shows a persistently rising pulse rate and falling hæmoglobin, surgery should be evoked promptly. I suspect that many of our deaths

in the past have been the result of undue hesitation on the part of the physician, hoping against hope that the next hour or so will see the patient rounding the corner.

If we could tackle the victim before he reaches the stage of collapse and give him rapid transfusion before and during the operation, and continue with drip transfusion after the operation, surgical results would improve and lives would be saved.

A few words in conclusion on surgery in relation to recurrent hæmorrhage from chronic ulcer. If we are satisfied that there is a chronic ulcer, be it in the stomach or duodenum, and if severe hæmorrhage has occurred twice in the past, I have no doubt that surgery should be instituted in the quiescent period and the source of danger removed by one or other surgical manœuvre. At once, however, the query arises—how do you know that the ulcer is, in fact, chronic? In at least 90% of cases the history is in keeping with the findings and one is in no doubt, but we do meet the 10% where the remarkable absence of history of recurrent indigestion suggests that there is merely an acute ulcer unsuitable for surgery; yet later investigation or even autopsy may reveal a large chronic ulcer as the source of the hæmorrhage. I am sure that this error is largely due to the low intelligence of a certain class of patient, rather than to any peculiar absence of symptoms. I have never met it in the intelligent but only in the classes from whom any history is difficult to elicit. However, the difficulty is, in fact, there. Again, if there has been a history of recurrent symptoms pointing to chronic ulcer and if the presence of a chronic ulcer be confirmed by X-ray, and if the patient be over 55 years of age, or if he has premature arteriosclerosis even though he be younger, then a single hæmorrhage would be, to my mind, an indication for operation when he has recovered from its immediate effects. The few surgical fatalities I have seen from operating on what might be called the "cold stage" of chronic ulcer have almost always been due to the poor general condition of the patients. They have usually leaked blood off and on for months, they are anæmic, the blood urea is raised and there is to be found a disturbance of the serum proteins, notably a fall of the albumin component thus upsetting the normal A/G ratio. These patients look tired, they often have swollen ankles at night, they are hypotonic and the blood pressure is usually in the lower regions of the normal or even subnormal. No matter how anxious such a patient may be to get on with the operation, his persuasion must be resisted firmly. A fortnight's rest in bed, correction of the anæmia, the administration of a high protein diet, or, if necessary, a mixture of amino acids, may make all the difference between life and death when it comes to surgery.

Curare.—My last point is a warning in relation to curare. In the patient such as I have depicted, or in one who is bleeding, I believe that there is a danger in using this drug. It is never necessary in the hypotonic individual. To produce complete flaccidity of the skeletal muscles in an individual whose systolic pressure is probably in the region of 100 or 110 is to invite such pooling of blood in the muscles that although the operation may be technically a success, the patient may die on the table of peripheral circulatory failure.

Mr. Norman C. Tanner: Gastroduodenal bleeding as a surgical emergency resolves itself into three problems:

(1) For *which* bleeding gastroduodenal lesions is emergency surgery indicated? (2) *When* is emergency surgery required? (3) What surgical technique is appropriate when operating for gastroduodenal bleeding?

(1) I will commence by giving a list of the causes of massive gastroduodenal hæmorrhage which I have encountered during the years 1941–1949 at St. James' Hospital, Balham.

TABLE I.—CAUSES OF GASTRODUODENAL BLEEDING (CASES) 1941–1949

Gastric ulcer	364	Simple gastric neoplasm	5
Duodenal ulcer	258	Gastric diverticulum	1
Anastomotic ulcer	40	Pancreatitis	2
Œsophageal ulcer	2	Carcinoma of pancreas	2
Gastritis	53	Aneurysm of aorta	1
Carcinoma of the stomach	29	Uræmia, chronic nephritis	1
Portal hypertension	31	Uncertain, duodenal diverticulum, &c.	44
Hiatus hernia	3		
		Total	836

We will group the first five together, for they all present with similar histories, so that preoperative differential diagnosis is uncertain, and the treatment is similar. In this group I have no doubt that surgery must play a most important part, which I will discuss later.

Carcinoma of the stomach.—Bleeding from operable gastric carcinoma usually ceases spontaneously, and so I prefer to treat these cases medically in the first instance, and then by transfusion and feeding get them into good enough condition for really radical surgery. All those cases of gastric carcinoma which I have found it necessary to operate on as an

emergency, because bleeding did not cease spontaneously, have proved to be inoperable. On the other hand half of the total group were resectable later.

Portal hypertension.—This condition is better treated medically in the first instance, for the majority will cease bleeding spontaneously in the first incident of bleeding. If necessary the balloon of an altered Miller-Abbot tube (Figs. 1 and 2) may be placed in the lower

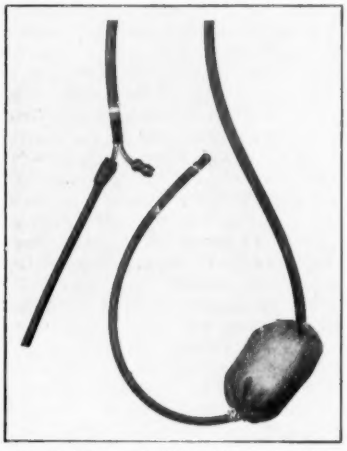


FIG. 1.—Balloon of Miller-Abbot tube altered for use in lower œsophagus.

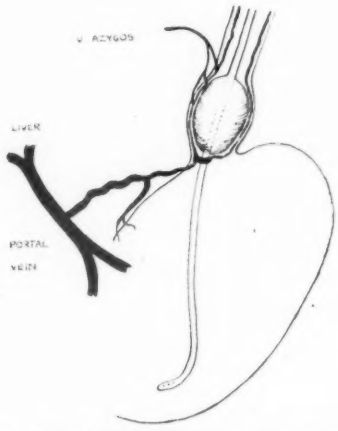


FIG. 2.—The distended balloon obstructs the collateral circulation from the gastric to the azygos veins.

œsophagus, as recommended by Rowntree (1947). However, some will bleed to death; in fact all of my cases except a few dealt with by interval surgery have eventually bled to death, and so urgent surgery may be indicated. I do not pretend to have the surgical answer to this problem, but I will show later a new emergency operation which I believe may be useful in the treatment of bleeding œsophageal or upper gastric varices.

Hiatus hernia.—Emergency surgery is not, as a rule, advisable for this condition, for the bleeding lesion is often from a peptic œsophagitis, which is unapproachable by the abdominal route.

I have never found it necessary to operate on *simple gastric neoplasm* or *gastric diverticulum* as an emergency.

Pancreatitis and carcinoma of the pancreas have both led me or one of my team to operate as an emergency, but in no case did we find that our surgery influenced the bleeding.

(2) *When is emergency surgery indicated?*—This problem naturally involves the peptic ulcer—gastritis group almost exclusively. It is certainly the most important group for it accounted for some 85% of the incidents of bleeding in my series. Opinion on when to operate is sharply divided, and will remain so because what may be the correct course for a physician in one clinic may be incorrect for one working under different circumstances or with different facilities.

Broadly speaking one of the following courses is open to the clinician.

(*a*) To treat all cases of massive gastroduodenal hæmorrhage medically, and only operate on those who seem certain to die unless surgery is invoked. This course results in late surgery on rather debilitated cases and so it *entails* a high operative mortality. On the other hand no case which would have recovered naturally will lose his life because of unnecessary surgical interference. It must also be admitted that with modern medical care and blood transfusion, some patients can be kept as a fair operative risk for several days. On the other hand some cases will die of bleeding while the physician makes up his mind and a large number of those who would have died under pure medical treatment will still die, because the surgery was late.

(*b*) The second course, and the most generally acceptable nowadays, is "selective surgical intervention", a very rational course which owes its acceptance in England in no small measure to the work and writings of Sir Gordon Gordon-Taylor. Under this regime certain criteria which are known to indicate a dangerous form of bleeding are also indications for early surgery. In particular, patients over 50 who have severe repetition of bleeding or who bleed persistently are operated upon.

(*c*) The third course is the "Finsterer" method. This policy, advocated by Finsterer

(1947), is as follows: If a patient with a history of chronic peptic ulceration is admitted with a severe hæmorrhage he is operated on at once. Finsterer argues that such early surgery carries little more risk than interval surgery, and the patient with chronic ulceration needs an operation anyhow. If, on the other hand, the patient has only a brief history or no history of ulceration, he is treated conservatively, but if bleeding is repeated or continues, exploratory operation is at once undertaken.

Now we are all aware that figures are produced which appear to prove one or the other the optimum course to follow. Obviously different types of cases, different facilities and different degrees of enthusiasm account for the varying results. In 1941 it occurred to me that if one large hospital, with a fairly uniform series of patients and facilities, were to keep careful record of each case, standardize the main treatment, but vary the extent to which surgery was employed, then some new light might be shed on the subject. Therefore with the co-operation of the physicians at St. James' Hospital, all cases of gastroduodenal bleeding were admitted to my medical or surgical gastric ward. A standardized treatment regime was laid down to eliminate as many variables as possible. The details need not concern us now (*see* Simpson-Smith Memorial Lecture, Tanner, 1949). The surgical policy was changed at certain definite times, and the results may be seen in Table II.

TABLE II.—PEPTIC ULCER AND GASTRITIS GROUPS
(748 *Incidents of Bleeding*)

		No. of cases	Over 60	Operated on	Overall mortality	Average age of patients who died
Selective surgical intervention	Period No. 1: 1941 to 1943—operation avoided as far as possible	193	33%	5%	10%	62
	Period No. 2: December 1943 to June 1944—operation earlier, always gastrectomy	60	33%	15%	20%	62
	Period No. 3: June 1944 to December 1947—operation early, simplest to stop bleeding	312	35%	11%	11%	65
	Period No. 4: January 1948 to September 1949—"Finsterer"	183	42%	60%	7%	66

In the last group we operated on 60%, that is 110 of the 183 cases. I purposely avoid putting in the operative mortality, although it was low, because I am not so much interested in the operative mortality as in seeing that the largest possible number of cases who enter bleeding leave the hospital alive. The overall mortality is more important than the operative one. The operative mortality depends so much on the type of risk accepted, and if I have too tender a regard for it, then I shall be afraid to try and save the patient almost moribund with hæmorrhage.

The table also shows that the cases were of great average age, in fact it is the oldest group of such cases ever recorded. The patients operated on varied up to the age of 81, and incidentally this patient recovered. I make a special note in the table of the average age of the patients who died, for if emergency surgery led to the loss of young patients unnecessarily, we would abandon surgery. It is evident that it does not do so, the youngest death in the latest regime being 58. Of course we used some judgment in the Finsterer regime. For example, during the last period we had 3 cases of hæmorrhage from chronic duodenal ulceration in patients under 17 years of age, and none of these was operated on as an emergency. We were justified in our decision not to operate by the lower mortality in these youthful cases. In the last 501 cases of ulcer hæmorrhage in this series, we have not lost a patient under 40 years of age. Similarly we judged occasional patients with extreme lung disease, adiposity, &c., to be a better medical than surgical risk, and discarded the Finsterer ruling for them. I have not time to go into the numerous coincidental lesions these patients suffered from, but 4 had carcinoma elsewhere, there were several cases with paralysis agitans, tabes dorsalis, hemiplegia, rheumatoid arthritis, ulcerative colitis, &c., and one case each of tetany, advanced myxœdema, severe burns, and hæmophilia. Incidentally, the hæmophiliac had a gastric ulcer and recovered first under the medical regime, but later came in during the surgical regime and had a successful gastrectomy by Mr. Desmond.

(3) *What surgical technique is appropriate for these cases?* There is no satisfactory emergency abdominal operation for the patient with bleeding œsophageal varices and I have given much thought to this subject. An operation similar to one I have used as an interval operation for the condition would probably meet the case, and I advance

it tentatively. I call it "transgastric porto-azygos disconnexion". The cause of the œsophageal and gastric varices which are the source of the hæmatemesis in portal hypertension is the collateral circulation between the portal and azygos systems of veins and the object of the operation is to interrupt it below the varices, thereby reducing the pressure in the varices from that of the portal, to that of the caval circulation (Figs. 3 and 4). Periœsophageal venous transection alone is inadequate, and impractical as an emergency proceeding. It is necessary that the emergency operation be one which can be performed by an upper abdominal incision, such as that used in exploring a case of hæmatemesis of unknown origin. Therefore I suggest (1) gastric transection and resuture to interrupt the venous circulation in the stomach (Fig. 5); (2) division of all the vasa brevia to the upper part. This entails lifting the stomach forward after transection and dividing the occasional vasa brevia which run up the posterior wall of the lesser sac from the splenic trunk; (3) division of the left gastric pedicle, carefully sparing only the left gastric artery, in order to preserve a blood supply to the cardiac end of the stomach, but of course dividing the descending branch of the left gastric artery. Thereby there is complete division between the portal and azygos circulations (Fig. 6). An additional advantage is that the left gastric artery no longer intro-

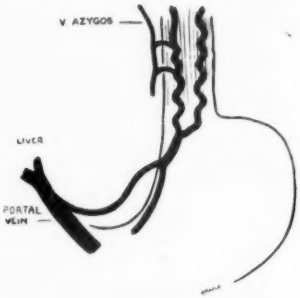


FIG. 3.—The œsophageal collateral circulation in portal hypertension.

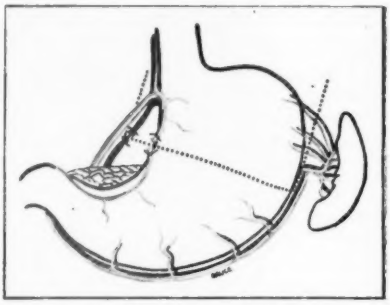


FIG. 4.—The points of porto-azygos disconnexion.

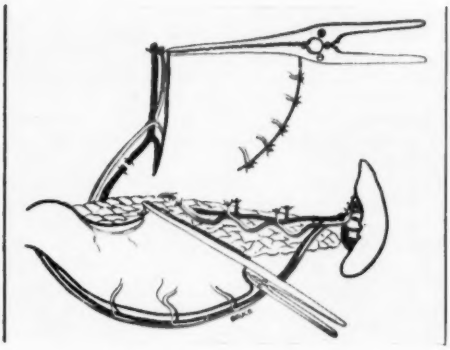


FIG. 5.—Division of splenic artery, vasa brevia and left gastric vein.

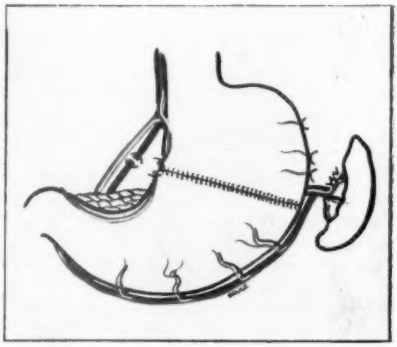


FIG. 6.—Porto-azygos disconnexion completed.

duces blood into the portal system and I have also on one occasion tied the splenic artery which reduces still further the inflow in the portal circulation. The diminution of the arterial inflow to the portal circulation thus compensates for the loss of the gastric collateral venous circulation.

How long its effect will last I do not know, for *some* fresh collaterals will eventually grow across the anastomosis. In the two cases on which I have performed this operation no ascites occurred and no recurrent bleeding thus far, but both are under a year since operation. Even if cirrhosis of the liver is found at operation careful search for an ulcer must be made, for such ulcers, in a hypertensive medium, are prone to bleed and I have three times performed gastrectomy for duodenal ulcer associated with hepatic cirrhosis.

Operations for bleeding peptic ulcer and gastritis.—Should one do the smallest operation possible, or a gastrectomy, for ulcer? If one is well acquainted with gastrectomy for ulcer, particularly for difficult duodenal ulcer, then I believe that gastrectomy is best, and that is the operation I now perform.

All cases are operated on under local anæsthesia. A few are too ill for general anæsthesia and local appears to upset them least. Its universal use also removes a variable—that of variable forms of anæsthesia—from our series.

(i) *High gastric ulcer.*—For this we perform a Pauchet modification of the Billroth I operation, removing a wedge-shaped piece of the lesser curve. The resected specimen obtained by such a procedure is well shown in Fig. 8.

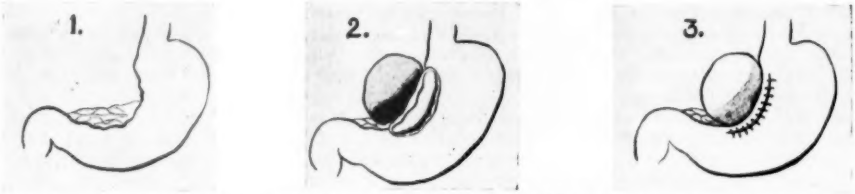


FIG. 7.—Massive gastric ulcer. The ulcer is "pinched off" and the ulcer edges trimmed and closed.

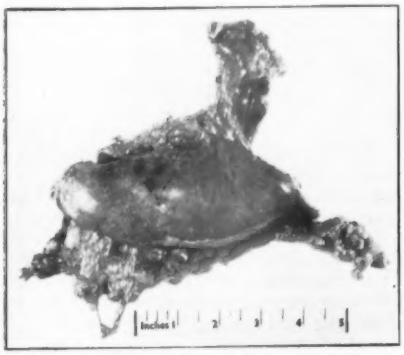


FIG. 8.—Resected stomach obtained after a Pauchet modification of Billroth I gastrectomy.

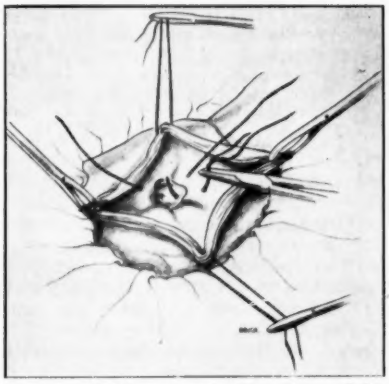


FIG. 9.—Duodenotomy. The edges of the ulcer crater are closed with deep silk sutures.

(ii) *Massive gastric ulcer in debilitated patients.*—Occasionally extremely fragile or aged patients suffer massive bleeding from a giant gastric ulcer which penetrates the liver and/or pancreas. In 3 or 4 grave cases of this type we considered that the patient might withstand minimal interference, but no gastrectomy, and the ulcer was too big to contemplate local excision. In these cases, we separated the ulcer from the liver or pancreas by "pinching off", taking great care not to damage the ulcer base (Fig. 7). The edges of the large hole left in the stomach were carefully sutured—taking care to make the sutures deep enough to get the whole of the ulcer edge. Two of the cases as a result had a stenosed stomach and gastrojejunostomy was done, but all recovered.

(iii) *Duodenal ulcer.*—For a time, during 1948, we made a longitudinal incision in the duodenum, closed the ulcer crater with deep sutures (Fig. 9), and after closing the duodenum longitudinally—to narrow it—performed a gastrojejunostomy. We had three recurrent hæmorrhages following this, one being fatal, but it undoubtedly saved lives on the whole. However, this year we have performed gastrectomy for duodenal ulcers and have no cause to regret our decision. I must emphasize that much experience of the dissection of chronic duodenal ulcer is necessary before embarking on gastrectomy for bleeding duodenal ulcer.

(iv) *Gastrojejunal ulcer.*—For this we open the stomach and occlude the bleeding point, and return later for gastrectomy, vagotomy or both. Occasionally, in a good-risk case, emergency gastrectomy is advisable.

(v) *Gastritis.*—Before deciding that bleeding is gastritic in origin, the most careful palpation and inspection of all parts of the stomach are necessary. The site of ulceration may merely show a blush, or local vascularization, or a little fixity of the serosa on the muscularis. On palpation the ulcer may not be felt and sometimes the sclerotic vessel in the crater is felt before the crater itself. I used to tie the right and left gastric, and right and left gastro-epiploic vessels, if at laparotomy no ulcer or other cause of bleeding was found, and yet massive hæmatemesis had occurred. In nearly every case this succeeded, but in a recent case of erosive gastritis in a youth aged 26 it failed. In his case, after he had had thirty-three pints of blood, on the tenth day, we had to operate a second time and perform a gastrectomy; this was followed by recovery. This case persuades me that if bleeding is of really great severity, and no lesion is found, then gastrectomy is advisable, for it removes four-fifths of the erosive area and partially devascularizes the remnant. If bleeding is only moderate, then I would still merely ligate the four main gastric vessels.

There are three further points. The surgical series requires that an experienced surgeon be continuously available. A good deal of the surgery has been done by my Assistant, Mr. A. M. Desmond, and some cases by my registrars, Messrs. W. W. Davey, C. M. Craig, and P. B. Counsell. Although of course the surgical regime requires vigilance it is not so anxious, nor does it involve so much nursing as the medical regimes. Great enthusiasm is required for good results by either method. Secondly I do not consider that we have in any way solved our problem. I have proved that our results have improved since we undertook much more frequent surgery for hæmatemesis and melæna. To see if this is accidental we intend to revert for a period to selective surgical intervention, in order to study the result of the change back. There is, however, one great advantage in this frequent surgery. When we discharge patients on whom we have performed a gastrectomy for hæmatemesis, most of them are rid of their ulcer trouble for ever. When we discharge them after conservative treatment, we know that many will return with bleeding, and some will die of it.

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Mr. Ivor Lewis: Patients with hæmatemesis should be admitted to the medical wards and the ideal combination is a keen young physician and a somewhat reluctant surgeon.

What we require in the management of hæmatemesis is a differential *prognosis*—to pick out certain groups where medical mortality is specially high. This has not yet been achieved. My own rough guide is that operation should be considered in all patients over 40 with a hæmoglobin under 40%, particularly if the hæmorrhage recurs, or there has been persistent pain. Avery Jones has shown that patients with hæmatemesis from duodenal ulcers and chronic gastric ulcers, if they are over 50 and have a sharp recurrent hæmorrhage, are more likely to die than to recover in spite of transfusion and the best medical treatment. As for the group under 40 it must be accepted that the hazard of an emergency operation is likely to be higher even in the best hands than the low 2 to 3% of good medical treatment. This does not mean that the physician or the surgeon should adopt a wooden attitude just because the patient is young; to relate that a patient bled so copiously and repeatedly as to need 20 pints of blood is more of a tribute to the patient's fortitude than to the doctor's good sense.

At the North Middlesex Hospital we admit about 120 cases of hæmatemesis and melæna per annum. Seldom a year passed without one or two young men of 30 being among the deaths and we would now consider operating even in these younger patients, when they have already had, say, 10 pints of blood.

Is it acute or chronic? Duodenal or gastric? I have operated in over 50 cases of hæmatemesis and have, for my own edification, compared our pre-operative diagnosis with the operative findings. Whether duodenal or gastric?—correct in 60% of cases. Whether acute or chronic?—correct in 60% of cases also. In other words, apart from cases with an X-ray which is both positive and recent, the opinion is little better than tossing a coin. This shows that the old injunction that you should only operate "where it is known that the patient has a chronic ulcer" is not very valuable except for the small number who have recently been X-rayed. Similarly the tag about the patient who is arteriosclerotic is not very important—the only artery that matters is the *open* one, and this is always sclerotic in the base of a chronic ulcer.

When to operate? The surgeon would like to operate as soon as the hæmorrhage recurs and before the patient collapses again. The houseman is usually phoned to "come at once as the patient has just vomited 2 pints of blood and is cold and clammy". It is not generally appreciated that the actual hæmorrhage precedes the summons by perhaps an hour or two. It is the *vomiting* with its commotion and straining which seems to precipitate the collapse.

I have found it a useful practice when on the look-out for a critical relapsing hæmorrhage to leave a Ryle's tube in the stomach (to the 2 rings) and have the nurse take a sample every half-hour. This simple measure will give the signal long before any sign. During the period of watching there is one very important thing to do. That is to transfuse the patient slowly if his hæmoglobin is under 40%. And there is one other thing still more important in my opinion: *not* to transfuse him if his hæmoglobin is over 50%. The blood should be held in reserve; if the hæmorrhage does not recur he will not need it; if it does, he will need it all, before, during and after the operation.

Preparation for operation.—The surgeon should have nothing to do with the physician who calls him only as "a last desperate resort", with the patient cold, pulseless and uræmic. In reasonable cases after a sharp hæmorrhage it may take anything from two to twelve hours to make the patient fit for operation. It is wrong to think that this process can be indefinitely hurried by giving the patient still more blood, more rapidly—a common error. A circulation which has been depleted for some time should be restored quickly, but not at one fell swoop. Only in rare exceptions should blood be given faster than about a pint an hour, even pre-operatively. Very few of my patients have had more than 5 pints of blood from the moment operation was decided on—perhaps 2 before, 2 or 1 during, and 1 or 2 after, the operation. There are two provisos regarding the surgeon who undertakes these cases: (*a*) he must be able to do an ordinary gastrectomy soundly and well in little over the hour, and (*b*) he must be prepared to deal with these cases any time of the day or night. Most of mine have been done between midnight and 3 a.m.

What to do (*a*) *when you find the lesion;* (*b*) *when you cannot find the lesion.* (*a*) In my opinion the minimum requirement in dealing with a bleeding artery in a peptic ulcer is (1) to ligate the vessel, and (2) to exclude it from subsequent contact with gastric juice. It must therefore not be thought that operating on hæmatemesis is synonymous with gastrectomy, a point so insisted on by Sir Gordon Gordon-Taylor. My practice is as follows:

In chronic gastric ulcer: gastrectomy with removal of the ulcer. (But if the ulcer is large and penetrating, its base is left in situ, and the artery under-run proximally and distally.)

In chronic duodenal ulcer; ligating the artery (gastroduodenal usually) both sides, plus gastrectomy or at least exclusion.

In subacute or acute gastric ulcer: elliptical resection of the ulcer.

(*b*) What does one do where one cannot find a lesion by sight or feel? Either (1) close the belly, or (2) open the stomach and find the vessel. Usually I find it more satisfactory to do the latter, having gone so far. It is a comfort to know the transfusion will stay put. Only in one case has the lesion not been apparent. The mortality for the cases operated on for bleeding peptic ulcer has been 15%. Looking back I consider several of the deaths should have been avoided. 15% is a high mortality for gastrectomy—about five times more than for "cold" gastrectomy. But the mortality for this group of cases, without operation, is over 50%.

Finally I would recall the simple fact that what these patients are suffering from is a *secondary* hæmorrhage, and that the bleeding artery is often as large as the radial.

Mr. A. M. Desmond: In presenting my personal operative results it should be emphasized that I was but one unit in a co-ordinated team under Mr. Norman Tanner especially trained to deal with gastroduodenal hæmorrhage.

My results in 53 cases are shown in Table I:

TABLE I

Cause	No.	Gastrectomy	Simple procedure	Deaths	Remarks
Gastric ulcer	26	22	4	2	1 death followed simple procedure 1 followed gastrectomy
Duodenal ulcer ..	16	16	—	—	—
Stomal ulcer	1	—	1	—	Bled post-operatively. Subsequent vagotomy
Erosive gastritis ..	2	1	1	—	Proven cases
No abnormality found	4	—	4	—	G.U. discovered later, by gastroscopy in one
Carcinoma of pancreas	1	—	1	1	Ligature of gastroduodenal artery and gastro-enterostomy performed. Hæmorrhage not controlled
Portal hypertension ..	1	—	—	1	Ligature of coronary vein. Bleeding not controlled
Uræmia	1	—	1	1	Bilateral pyonephrosis
Carcinoma of stomach	1	—	—	1	Abdominal total gastrectomy

Some of these cases were operated upon before 1948 under the principle of selective surgical intervention. Others, in the last two years, were treated according to the principles of Finsterer.

In 4 cases, no lesion was found at operation and vasoligation was performed. In one a gastric scar was revealed on subsequent gastroscopy. An abdominal total gastrectomy was performed for hæmorrhage from a leather-bottle stomach with fatal result.

Carcinoma of the pancreas as a cause of hæmatemesis is not well recognized. We have experienced two cases. In my case the tumour had ulcerated the duodenum, and in spite of a gastrojejunostomy and ligation of the gastroduodenal artery the patient bled to death. In the other case, the tumour had involved the posterior gastric wall.

The deaths in the gastric ulcer group:

Case I.—At operation a large pyloric ulcer was freed from the liver and the stomach sutured. Obliteration of the lesser sac was noted.

4th day: He vomited blood.

6th day: He developed intestinal obstruction due to old adhesions and succumbed after further aparotomy.

P.M.—There was a giant gastric ulcer with erosion of the splenic artery. This ulcer had not been demonstrated at operation (Fig. 1).

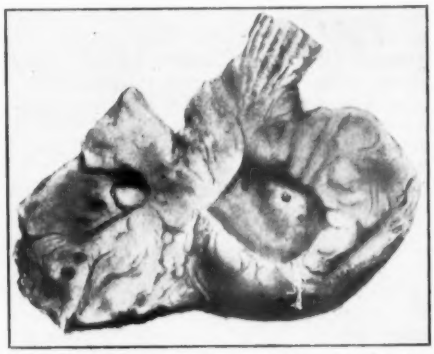


FIG. 1.—Autopsy specimen of stomach showing giant gastric ulcer eroding the splenic artery.

Case II.—Admitted to general medical ward as carcinoma of lung. Found to be having melæna stools and on questioning admitted to constant melæna for one week. Suffered from severe chronic bronchitis and emphysema.

At operation multiple small subacute gastric ulcers. Gastrectomy performed.

Died from bilateral bronchopneumonia on 12th post-operative day.

Inspired by Sir Gordon Gordon-Taylor, the most favoured method of treatment in this country has been by selective surgical intervention.

After studying our own case histories I would like to emphasize the importance of pain in influencing the decision to operate. The following would suggest that surgery should be considered: (1) A particularly severe bout of pain immediately preceding the hæmorrhage especially if associated with vomiting. (2) Radiation of pain to the back between the "shoulder blades" or to the shoulder tip. (3) Persistence of pain after the hæmorrhage.

In most cases the pain disappears almost as soon as the hæmorrhage occurs. Sometimes it does not do so, or the relief is but temporary and pain recurs soon afterwards.

Another highly dangerous type of case is the one who, whilst in hospital under treatment for ulcer, suffers a severe hæmorrhage. The reason for these seems to be associated with the activity of the ulcer. There is a type of ulcer in which spreading necrosis of the gastric or duodenal wall occurs, and these ulcers may perforate or rapidly erode a large vessel.

Two examples of such ulcers occurred in this series:

A man aged 35 came to the clinic with a two-months' history of vague dyspepsia, but with some pain in his back. A barium meal was taken but before it was seen he was admitted with a perforated gastric ulcer which was sutured.

Five days later he commenced having large hæmatemeses which failed to respond to conservative measures.

On the 6th day the abdomen was re-opened and an enormous saddle ulcer was freed from the pancreas and the stomach sutured. He did well, and as a gastroscopy performed six weeks later showed a large ulcer still present, a gastrectomy was performed.

A man aged 66 was operated on for a perforated gastric ulcer. The ulcer was small and on the anterior wall of the lesser curve.

Post-operative urinary retention necessitated a cystotomy. On the twelfth day he had a severe hæmatemesis and melæna.

Conservative treatment was considered advisable, but in spite of repeated transfusions, melæna continued on and off.

On the 37th and 38th days he suffered severe collapses with melæna. On the 40th day the abdomen was re-opened. Practically the whole posterior gastric wall was replaced by an ulcer penetrating the posterior abdominal wall. It was freed and the stomach sutured and a drainage tube inserted. A gastric fistula developed and a feeding jejunostomy was formed. The fistula healed on the 1 th day and he recovered well. Prostatectomy was later performed by Mr. H. K. Vernon and he remains in excellent health.

A high blood urea is a grave prognostic sign but we feel that it should not constitute a deterrent to surgery. We have successfully operated on 8 cases with values over 120 mg.%, three cases having values over 150. We feel that a patient with severe azotæmia is better able to tolerate a surgical operation under local anæsthetic than he is a further severe hæmorrhage.

With increasing numbers of operated cases there has naturally been an increase in diagnostic errors, although the percentage is roughly unaltered. In an attempt to obviate these errors we have resorted to emergency gastroscopy and not only have we clarified the situation in many cases, but have so far encountered no untoward results. The discovery of an ulcer does not necessarily mean an emergency gastric resection is performed. If a large ulcer with a sealed vessel is seen, however, we would operate within twenty-four hours.

As soon as the decision to operate has been made the patient should be brought as quickly as possible to the best possible state to withstand operation. Three points must be emphasized:

(1) The patient's condition may improve so dramatically that one may be sorely tempted to postpone operation. This would be ill-advised as the rapid increase in blood pressure may precipitate a further hæmorrhage.

(2) Resuscitation must not be too vigorous as a further hæmorrhage may occur before the patient has reached the operating theatre.

(3) It would be better if facilities permit to carry out the final resuscitation in the operating theatre or anæsthetizing room.

Dr. F. Avery Jones: From a personal experience of over 400 cases of frank hæmatemesis and melæna treated before 1945, I became convinced that there was scope for surgery in the management of this emergency. The cases which carried a particularly high mortality were those over middle age, who had a probable chronic ulcer, and who bled again after admission to hospital. Some of these cases had other serious medical complications which would preclude surgery but there was a small residue of cases where emergency surgery might have been successful. Since 1945, emergency partial gastrectomy has been performed in patients falling within this category and so far 23 cases have been operated on with 4 deaths. The expected mortality under medical treatment would have been at least 12 and probably more. The ages of these cases are set out in the following table.

TABLE I

	Emergency partial gastrectomy				Laparotomy			
	Cases	(Ages)	Died	(Ages)	Cases	(Ages)	Died	
1945	3	(51, 57, 65)	—		1945	3	(17, 41, 47)	—
1946	2	(54, 66)	—		Part 1949	3	(35, 47, 64)	—
1947	7	(56, 56, 59, 62, 66, 70, 75)	2	(62, 75)				
1948	6	(46, 48, 51, 57, 61, 62)	—					
	18		2					
Part 1949	5	(19, 70, 70, 68, 73)	2	(70, 68)				

It might have been thought that successful surgery which reduced the expected number of deaths on past experience would have reduced the overall mortality since 1945, but the following table shows that the mortality has, in fact, not been reduced. The explanation for this lies in the higher proportion of admissions of patients over 70. Over this age, the

mortality becomes very much increased. Under the age of 70, mortality has actually declined in recent years.

TABLE II

	Hæmatemeses		Peptic ulcer group	
	Admitted	Deaths		Deaths under 70 years of age
1940	58	5		4 in 53
1941	58	5	= 7%	5 in 131 = 7%
1942	82	5		4
1943	102	4	= 6·5%	3 in 194 = 5%
1944	113	10		7
1945	135	9	= 8%	6 in 216 = 5%
1946	120	12		5
1947	101	8	= 8%	2 in 180 = 4%
1948	122	10		5
	891	68		41 in 774
1949 Part ..	106	8		0

TABLE III

	Aged 70 and over		
	Admitted—% of total admissions		Deaths
1940	5		1
1941	3	6·5%	–
1942	6		1
1943	9	10%	1
1944	12		3
1945	13	15¼%	3
1946	26		7
1947	25	19%	6
1948	18		5
	117		27
1949 Part	23 (22% approx.)		8

It is likely that the maximum benefit from partial gastrectomy for bleeding peptic ulcer will be between the ages of 45 and 70. Over 70 there are so often serious associated medical conditions which militate against successful surgery.

Section of Laryngology

President—R. D. OWEN, B.Sc., F.R.C.S.

[*November* 4, 1949]

The Problem of Hypopharyngeal Carcinoma. [*Abridged*]

PRESIDENT'S ADDRESS

By R. D. OWEN, B.Sc., F.R.C.S.

THE anatomists label all structures from the level of the soft palate to the pharyngo-œsophageal junction as "pharynx"; but I like the old terminology of "hypopharynx", by which I mean the pyriform fossæ and postcricoid space, down to the entrance of the œsophagus.

I do not propose to discuss carcinomatous lesions involving the epiglottis, aryepiglottic folds, and the lateral wall of the pharynx above the laryngeal opening.

In a discussion in this Section on malignant disease of the pharynx (Simpson *et al.*, 1948) it was shown that cancer of the lower pharynx still remained a difficult proposition. Negus (1948) states regarding prognosis, that extrinsic cancer is amenable to extensive operation in a limited number of cases only, and rarely with a permanently successful result. Irradiation offers no better prospects.

The choice of treatment is not easy to decide upon. When we are confronted by an early operable case there is a tendency to take the path of least resistance and hand over the patient to the radiotherapist. Irradiation has been and is being tried in various forms, but still with limited success. It makes one wonder what constitutes the greater form of misery—to die with no attempt having been made to cure with radical surgery; the suffering that comes with the recurrence after radiotherapy; or the lot of a patient who has had a pharyngo-laryngectomy performed, and the suffering that follows when a recurrence appears, particularly before the plastic phase has been completed. The uncontrolled dribbling of saliva, and being without a voice to express one's misery, still remain a grim and sad picture.

Our sincere hope is that improvement in radiotherapeutic methods may one day reach the stage when pharyngeal cancer can be treated with greater confidence, and even make us forget about the necessity for radical surgery.

The history of the patient must be carefully taken and the significance of symptoms described as "catch in the throat" or "pricking sensations" must be appreciated.

This symptom of "pricking sensation" can be very confusing, as a common cause of discomfort in the throat is the retention of debris or pus, or even small calcareous deposits in the tonsillar crypts. It is very easy to clean out and empty the crypts, and then follow this by using the laryngeal mirror to examine the lower pharynx and the larynx. Having found a normal larynx and clear pyriform fossæ, without the retention of mucus in them, one may conclude that the cryptic activity in the tonsils is the cause of the pricking sensation.

Tonsils have been removed as being the cause of this discomfort, and within three months I have seen the patient referred because of dysphagia and glands in the neck, due to a postcricoid growth which was undoubtedly present at the time of the removal of the tonsils.

When the patient's throat symptoms are combined with voice changes, such as a moist, muffled tone, or huskiness, one immediately becomes suspicious of a laryngeal or a pyriform fossa lesion. Voice change, with a postcricoid growth, is, however, a late symptom. Yet it is sometimes amazing what an enormous mass can be present behind the cricoid with very little voice change, and even without the fixation of a vocal cord.

It is also true that dysphagia need not be very pronounced when the lesion is localized to the posterior or anterior wall of the hypopharynx, but when the spread is tending to become annular, then real dysphagia appears, with the usual squelching noise and a slight cough when attempting to drink fluids.

There are recorded cases of congenital narrowing of the upper gullet, without the history of dysphagia. Brown Kelly once showed a post-mortem specimen of a man of 35 who never complained of trouble in swallowing, and yet the lumen of the pharyngo-œsophageal junction had a diameter of only 4 mm. Chevalier Jackson made the observation that well-masticated food can pass through a lumen of 5 mm., and that a malignant stricture of a 3 mm. lumen will take food ordinarily eaten by the average man, provided it has been put through a sieve of 25 meshes to the inch.

It is little wonder that the general practitioner, when confronted by a dysphagic patient, can be misled.

It means also that indirect laryngoscopy is not always enough. The hypopharyngeal speculum, or the œsophagoscope, ought to be used when there is a doubt about the character of the pain or discomfort. This is the only way to try and establish an early diagnosis.

It is true that operation, in properly selected cases, is justified by results. As John Simpson said, the figures published by the late Mr. Colledge in 1943 still remain the peak to which this branch of surgery has been brought: That 13 out of 39 patients, i.e. 33%, were well, ten years after lateral pharyngotomy, and that out of 16 cases of pharyngo-laryngectomy, 6 (or 37%) were alive and well.

The radiotherapist cannot as yet produce figures comparable to those published by Colledge. Radiotherapy for cancer of the pyriform fossa, the postcricoid area, and the cervical portion of the œsophagus still proves to be disappointing though fairly good results are obtained in the vallecular regions, epiglottis, and the aryepiglottic folds, but not in the hypopharynx proper. That is why we have to continue to think in terms of radical surgery. The classification of neoplasms in this area is important, with an accurate picture of the localization and extent of the growth.

These essentials were discussed at a memorable meeting of this Section in December 1931 (*Proc. R. Soc. Med.*, **25**, 431).

The merits of plain excision on the one hand, and radium combined with surgery on the other, were discussed. That is nearly nineteen years ago, and as far as I can see, the problem remains the same to-day.

To-day we are of the opinion that under certain conditions the loss of the larynx is relatively of minor importance in a life-saving undertaking. The ideal, however, is to try and make certain that cases are brought to one's notice early enough to avoid the necessity of mutilating operations. We still have to admit that the net survival rate, even for treatable cases, is disappointing, and that the proportion of late cases coming for treatment is far too high.

What, then, are the difficulties that continue to make this hypopharyngeal problem so elusive? I believe that up to now we lack the courage of conviction. We refuse to recognize the fact that certain early signs and symptoms belong to a phase that ought to be regarded as precancerous. I know that the word "precancerous", in the pathological hierarchy, is not altogether popular, but there is no reason why the word should not be used, provided one knows its meaning. According to Professor Scarff it should be used to denote any condition of the tissue in which malignancy is more likely to occur than in normal tissue.

In a discussion that took place in this Section in February 1936 (*Proc. R. Soc. Med.*, **29**, 526), Mr. Negus described two cases of chronic hypopharyngitis that eventually developed postcricoid carcinoma. He went so far as to say that the right course was to excise that segment of the œsophagus before carcinoma developed.

Even in 1931 Mr. Negus emphasized the need of early diagnosis, and supported this teaching by mentioning the case of a patient with pain on swallowing, which was referred to the pyriform fossa. Direct examination showed raised small masses on the lateral wall of the pyriform fossa. Microscopical examination showed this to be a fibroma, with inflammatory infiltration. Mr. Negus performed a transthyroid pharyngotomy, which was a complete success. He made it clear that there were no malignant changes on examination of the specimen, but still he regarded it as precancerous.

That to me is the courage of conviction. In other words, whenever one is certain that a condition of hypopharyngitis is progressive, everything else being equal, it is one's duty to regard it as precancerous.

While dwelling on this precancerous problem, I shall refer to the Paterson-Brown Kelly syndrome—sometimes incorrectly described as the Plummer-Vinson syndrome. Paterson, in 1919, was the first to draw attention to the fact that the development of a postcricoid carcinoma, in women complaining of this syndrome, was far too frequent an occurrence to be a mere coincidence. Brown Kelly, in his Semon Lecture in 1926 said: "I think that the relation of pharyngo-œsophageal spasm to anæmia would be a fruitful subject for investigation, particularly when we consider some of the complications such as postcricoid carcinoma."

In 1939 R. R. Simpson, of Hull, stated that examination of the records of his cases suffering from this syndrome, where œsophagoscopy was carried out for dysphagia, revealed that at least 50% either had, or developed, a carcinoma. His figures, however, showed that the lower end of the œsophagus was more vulnerable than the postcricoid area. 10 out of 18 cases developed malignant disease; 4 postcricoid, 5 the lower end, and 1 the lower third—all of them complaining of simple achlorhydric anæmia and a long-standing "small swallow".

I cannot say that in my experience of the Paterson-Brown Kelly syndrome has the incidence of carcinoma as a complication been so high.

Ahlbom of Sweden, in his long series, appeared to have no difficulty in associating a proportion of carcinoma of the mouth, the pharynx and the œsophagus with the Paterson-

Brown Kelly syndrome, but no figures regarding the postcricoid lesion have been mentioned. Since then, Flett of Derby has stated that out of 100 cases which he followed up complaining of this syndrome, not one developed a carcinoma, but after communicating with him later I know that he has altered his opinion since then. Colledge, in his Lettsomian Lectures, mentions a case of a female with the Paterson syndrome and a postcricoid carcinoma, on whom he had performed a pharyngo-laryngectomy for the removal of the growth. This patient, ten years later, came under observation (at the Cardiff Royal Infirmary) with a carcinoma of the lower end of the œsophagus and the cardiac end of the stomach.

In August of this year I followed up the subsequent history of 34 female patients who had been in-patients at the Cardiff Royal Infirmary for investigation of the syndrome of dysphagia with anæmia. These patients had been admitted during the years 1934–35, and I am excluding all those who appeared during those years for the first time with a postcricoid carcinoma. I chose the years 1934–35 as we happen to have had an exceptional number of these cases during those two years. Also, now that fifteen years have elapsed it gives, in my opinion, a fair period to enable one to assess the course of events.

R. R. Simpson in 1939 said: "The few writers on this subject referred to the supervention of malignant disease as a possibility, but so far no attempt has been made to assess the frequency of this occurrence, despite its general recognition."

Of the 34 female cases that came under my care, all had direct œsophagoscopy performed on them, as well as the usual blood counts, and some had fractional test meals. They were diagnosed as cases of dysphagia with simple hypochromic anæmia. Direct examinations were carried out in order to dilate the cricopharyngeus web, to improve the swallowing, and in particular to try and assess correctly the mucosal changes.

The follow-up of these cases after fifteen years showed:

TABLE I

No. of cases seen during 1934–35	34
No. still surviving without any evidence of malignant disease	23
No. that developed a postcricoid carcinoma	5
No. not traced after 1939, but free from malignant disease up till then ..	6

I was surprised to see that so many of these women remained free from malignant disease. My impression had been that cancer occurred more frequently, but not in the high percentage mentioned by R. R. Simpson.

Of the five that developed a postcricoid carcinoma, Table II shows the varying periods at which this developed after direct œsophagoscopies, and this enables one to focus attention on the possibility of a precancerous condition in this syndrome.

TABLE II

Patient	No. of dilatations (direct œsophagoscopy)	Postcricoid growth developed	Age when developed
1	3 (1934, 1938, 1940)	1947	75
1	2 (1934, 1935)	1938	55
1	2 (1934, 1936)	1937	63
1	1 1935	1937	39
1	1 1934	1942	42

Out of the 23 classified as having no malignant disease, 12 of these women reported having had considerable benefit after dilatation. They swallowed solids easily for about twelve months to two years; after that symptoms gradually reappeared. They returned to a diet of soft food and liquids and any attempt at solids produced a choking attack. The following letter is typical of others sent to me from these patients during the course of the follow-up: "I received treatment at your Hospital in 1935 and 1945. After both occasions I enjoyed a period of two years of perfect swallowing but now the condition has gradually returned and I cannot go without the fear of choking during a meal when trying to swallow solids." 11, however, said that they are very much better and able to eat everything with reasonable care.

Their own doctors followed up the treatment of the hypochromic anæmia very conscientiously in the majority of cases, and I daresay that this, as well as the dilatation, has helped to bring about an improvement in so many.

But what about the 12 that continue to complain of the dysphagic symptoms? Is it the right treatment to encourage these women to come up for repeated dilatation? I have already mentioned that three direct œsophagoscopies during a period of six years made no difference to one patient, and did not prevent the appearance of a postcricoid growth thirteen years after the first dilatation. Would more frequent dilatations have succeeded in preventing malignant changes? At the same time the fact that 11 out of 23 are more or less symptom-free after one dilatation makes one hesitate in being dogmatic about the fact that hypopharyngitis is to be regarded as precancerous.

The question is whether these 12, whose ages average 64, are becoming more vulnerable to the development of hypopharyngeal cancer, or even the localization of cancer lower down in the œsophagus and why should the dysphagic symptoms reappear?

The results of the follow-up inquiry of these 34 females who were seen first in 1934/35 may be interpreted as follows: At the end of fifteen years, the proportion who had developed postcricoid carcinoma lies somewhere between 15 and 32%, assuming that the six who were not traced after 1939 can be regarded as free from cancer.

We know of no figures showing the incidence of the disease in the general population, but Stocks has shown (Statistical Review, part 3, text, 1940–45, Table LXXX) that the mortality rate from cancer of the pharynx in females since 1911 has not been greater than 25 per million at any age-group. 15 to 32% seems therefore a very high figure, and certainly suggests some extra risk of incurring the disease amongst people with dysphagia and simple hypochromic anæmia.

Mean ages of the groups are perhaps not the best approach to the study of the effect of age on prognosis, and in any case they should all be measured from the same point of time. One would like to measure them from the age at which the so-called "precancerous" state developed, but we do not know this, and the nearest approximation we can get to it is the age at which patients were first seen and dilatation was performed.

In the following table the three categories have been classified in 10-year age-groups, according to their age in 1934–35, when first seen.

TABLE III.—AGE DISTRIBUTION OF PATIENTS ACCORDING TO THEIR AGE IN 1934–35 WHEN FIRST SEEN

		Ages 30–	40–	50–	60–	Total
A.	With symptoms but no growth	4	3	4	1	12
B.	Without symptoms	2	8	1	–	11
C.	Developed growth	2	–	1	2	5
	Total	8	11	6	3	28
C.	as percentage of total.. ..	25%	—	16%	66%	

The figures are too small to draw any valid statistical deductions—the difference could have arisen by pure chance—but if the percentages should remain the same on a larger set of figures, or if the analysis was repeated on several series of patients with similar results, then it would be suggestive that it is after the age of 60 that the risk of growth developing becomes greatest.

In the present age distribution of Groups A and B, 50% of the 12 women with symptoms but no growth are now, in 1949, over 60, as compared with 64% of the 11 women who are free from symptoms. The actual age distributions are shown in Table IV and it will be interesting to follow the subsequent history of the two groups.

TABLE IV.—AGE DISTRIBUTION IN 1949 OF GROUPS A AND B

	Age 40–	50–	60–
A ..	2 (16·7%)	4 (33·3%)	6 (50·0%)
B ..	1 (9·1%)	3 (27·3%)	7 (63·6%)

My clinical conclusion is that 12 women whose ages average 64, and have complained of dysphagia for at least fifteen years, so far show no sign of malignant disease. 11 responded to treatment and are more or less symptom free. 5 developed postcricoid carcinoma; 3 after more than one dilatation. It is important to remember the insidious onset of cancer. These women, through the years, have schooled themselves to put up with this persistent, painless pushing down of food. Some become so accustomed to it that they regard it as normal. Then sudden serious attention may be drawn to it by some mischance when a bolus of food sticks in the upper food passage. A direct examination may be carried out with a view to dilatation and to assess the condition of the mucosal lay-out. At the same time a piece of mucosa may be taken for microscopical section and, more often than not, a report is returned,

showing that the appearance is not suggestive of neoplasm but more like inflammatory granulation tissue.

For years one can watch patients with this kind of history and the majority seem to go on without developing the complete picture of malignant disease—but they must be regarded as vulnerable and followed up if proper and early diagnosis is to be made.

Early diagnosis of carcinoma of the postcricoid space and the upper end of the œsophagus means the avoidance of the major and mutilating operation of pharyngo-laryngectomy.

If the mortality rate in this disease is to be reduced, the recognition of signs and symptoms suggestive of a precancerous condition are important, but I shudder to suggest that *all* these patients should be operated on during that phase, apart from having direct œsophagoscopy performed.

The series of malignant tumours that I have removed from the hypopharynx show certain variations in the clinical pictures. There is a marked clinical difference between the soft, spreading, ulcerative type (Fig. 1), which generally involves the postcricoid space and the upper end of the œsophagus, and what one may call the hard, scirrhous, infiltrating variety. With the former, secondary infection colours up the picture and metastases are more frequent, whereas with the latter, active ulceration is less of a feature, as is secondary infection, and secondary glands are not so frequent. Fig. 2 illustrates the endoscopic appearance of the soft ulcerative type. It is to be seen mostly in females who have had a postcricoid web for years. As already stated a number seem to improve after dilatation. Some, however, turn up two or three years later with a foul-smelling ulcerating mass involving the pyriform fossæ and both the anterior and posterior walls of the hypopharynx. The cords may be fixed and there may be further extension of the growth to involve the soft tissues of the neck, such as the thyroid gland, as well as secondary glands.



FIG. 1.



FIG. 2.—Endoscopic view of the "soft ulcerating type".

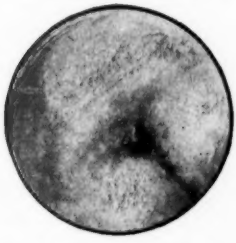


FIG. 3.—Endoscopic view of the hard rigid walls with a narrow lumen at cricopharyngeus level.

The other clinical endoscopic picture to be seen is the type where a direct œsophagoscopy has had to be repeated three or four times, and where, at the first dilatation, the so-called membranous web is not encountered. In these cases, even after four dilatations, improvement is not maintained. Instead of a web one meets a rigidity and firmness surrounding the whole of the hypopharyngeal wall as illustrated in Fig. 3. One may not see any mucosal changes, but if handled roughly there is a tendency to bleed.

Here the stenosis may be due to submucosal fibrosis. The anæmic picture associated with web formation is not always present and makes one conclude that this is another distinct

clinical type of postcricoid narrowing. It differs entirely from the "web" formation of the Paterson-Brown Kelly syndrome.

As an example of what I regard as the persistent or progressive fibrotic type, without malignant changes, I am reminded of a woman, aged 64, who was admitted as an emergency with a history of dysphagia for at least thirty years. Ten days before admission she found herself unable to swallow anything solid, and even fluids gave her the greatest difficulty.

On admission she was extremely dehydrated, frail and wasted. She looked anæmic, but the tongue did not show the usual glazed atrophic appearance, and the nails were not spoon-shaped. Indirect laryngoscopy showed nothing, apart from the retention of mucus in the pyriform fossæ. A direct œsophagoscopy showed marked rigidity and thickening of the hypopharyngeal wall, commencing about 2 cm. below the level of the arytenoids. The picture gave the impression of a circular stricture. In the very narrow lumen was found impacted a small foreign body, and this was removed without difficulty. Within a few months the same accident happened again from which she did not recover.

Post-mortem examination showed that there were two constricted areas, the centres being 3·5 cm. and 9 cm. respectively, below the laryngeal opening, the upper one being by far the most marked. To the naked eye the mucosa in the pyriform fossæ appeared normal, but in the postcricoid region it looked opaque and thickened. This latter appearance extended in a marked degree for about 12 cm., the rest of the œsophagus being normal. Histologically, at the site of the stricture there was marked infiltration with inflammatory cells, principally lymphocytes and plasma cells, but also a few polymorphonuclears.

The microscopical section, Fig. 4, showed that at one place the inflammation extended through the muscular coat, completely destroying the latter. Nearby, where the lesion was less severe, the muscle fibres were thin and there was fibrosis and inflammatory infiltration.



FIG. 4.—Low power.

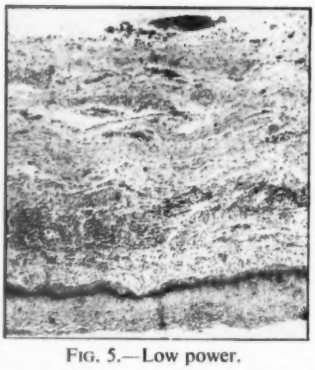


FIG. 5.—Low power.

Another section, Fig. 5, showed the part below the upper stricture, where the inflammatory infiltrations were more confined to the submucosa, and the muscle layer showing little infiltration and less atrophy.

In extent the fibrotic infiltration involved at least 9 cm. of the hypopharynx and the upper œsophagus, with the main stricture 3·5 cm. below the laryngeal opening. I feel it fair to assume that the whole of this segment must be regarded as more vulnerable than the rest of the œsophagus, and that had she lived, other changes such as malignancy might have supervened at any level within the 9 cm. There is no doubt that continued trauma to this inflamed mucosal surface, plus the unhappy fibrotic bed on which it lies, are factors that cannot be ignored in regarding this segment as precancerous.

In view of these clinical pictures that I have mentioned I would like to discuss the types of tumours operated on.

The soft ulcerating type when it involves the whole of the lumen and is not confined to the postcricoid plate is, as far as my experience goes, the most difficult to cure surgically. The presence of glands, however early, makes the prognosis much worse. Even after a very sweeping pharyngo-laryngectomy, and with the absence of secondary glands at the time of operation, recurrence may take place sooner or later. This happens either lower down in the œsophageal stoma or with secondary glands elsewhere. Even when a cut margin of an inch

has been allowed below the level of the growth, recurrence has taken place at the cut margin. This takes one's mind back to the possibility of segmental vulnerability due to chronic inflammatory infiltration of the œsophageal submucosa as shown in Fig. 5; in other words chronic hypopharyngitis.

A lateral pharyngotomy should never be performed on the soft ulcerative type, even if considered operable and localized to the postcricoid plate. A pharyngo-laryngectomy gives a better chance of a cure.

As for the hard infiltrating scirrhous variety, as shown in Fig. 6, here the thickening of the



FIG. 6.

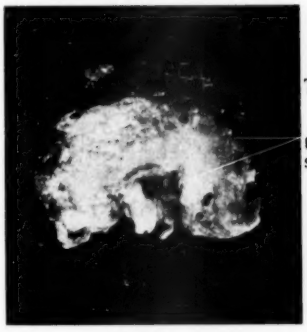


FIG. 7.



FIG. 8. × 60

œsophageal wall reduces the lumen to 2 or 3 mm. There is very little superficial ulceration and when the same segment is cut transversely, the submucous thickness of the wall compared with the degree of ulceration is seen (Fig. 7).

The tendency, when treatment is considered for these cases, is to advise removal by performing a transthyroid pharyngotomy, and in the majority there is no difficulty in peeling off the lower pharynx from the back of the larynx. When the whole segment is sectioned microscopically, one too often sees that only a small rim of healthy tissue remains beyond the limit of the neoplastic infiltration—far too small a margin for real safety (Fig. 8). This section illustrates the point. It so happens that this patient had been irradiated previously and the effects are well seen with some dead cancer cells.

I find it sometimes very difficult to be certain as to the type of operation that ought to be carried out, and I think it is fair to ask the question "How do we assess operability of a postcricoid neoplasm, and when do we consider the tumour as suitable for the operation of transthyroid pharyngotomy?" We know from the teaching of Trotter and Colledge that this operation is an excellent means of approach to growths involving the epiglottis, the lateral wall of the pharynx, and the aryepiglottic fold, but what about its suitability to lesions situated lower down in the postcricoid space and extending to the upper end of the œsophagus?

When one is faced with this type of growth, the question foremost in one's mind is whether the mass can be removed without sacrificing the larynx. Indirect examination with the laryngeal mirror may show free and mobile vocal cords and normal arytenoids. When this is the case, the tendency is to decide upon a transthyroid approach, particularly when glands in the neck do not appear to be involved. But mobile vocal cords and normal arytenoids are no guarantee that the hypopharynx can successfully be separated from the larynx.

There is nothing more embarrassing than, having started on a transthyroid pharyngotomy, to find when mobilizing the thyroid lobe that the growth has extended insidiously into the posterior edge of the lobe or on to the back of the larynx. The involvement of the gland under the edge of the thyroid isthmus generally means that the larynx is involved as well, and that the hypopharynx cannot safely be separated from the larynx. With this state of affairs, a transthyroid operation has to be converted into a pharyngo-laryngectomy, and this cannot be done unless care has been taken at the very beginning to fashion a skin flap in such a way as to enable one to prepare for the subsequent plastic repair.

The downward extension of the growth cannot always be judged by direct examination. While soft tissue X-ray can prove helpful one cannot be certain of the extent of the growth until it can be palpated by exposure. The size and the type of flap made at the beginning is therefore important.

Colledge made it a rule that neoplasms of the pyriform fossæ and advanced postcricoid growths required a pharyngo-laryngectomy, and it was his custom to fashion a flap for this operation by turning back large skin flaps from the mid-line of the neck, whether a gland dissection was necessary or not. I prefer, however, the large skin flap as suggested by Wookey, with a wide base hinged either on the right or the left side, behind the sternomastoid. There are greater advantages to be had with this exposure as a lateral pharyngotomy can be transformed into a pharyngo-laryngectomy should one find, half-way through the operation, that the larynx cannot be saved.



FIG. 9.

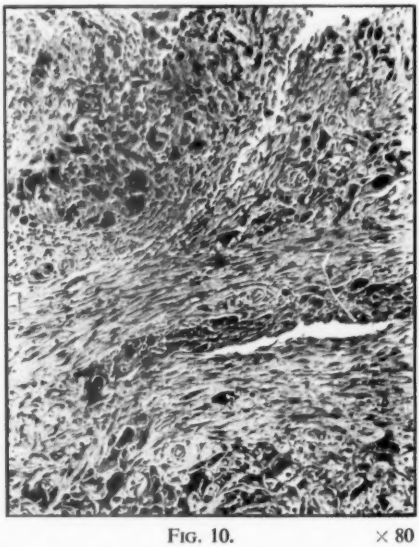


FIG. 10. × 80

Operative results.—I find that in spite of grading, the clinical soft, spreading, ulcerating tumour gives a far higher percentage of recurrences than the hard, infiltrating type, even when both are graded as 1.

The suggestion that it is unwise to advise radical surgery for the more anaplastic Grade 4 is not always true. Fig. 9 shows very superficial ulceration, beginning in one pyriform fossa with œdema of the aryepiglottic folds and extending downwards for nearly two inches. The section of this growth (Fig. 10) shows a carcinoma which here and there has differentiated into obvious squamous cells, but for the most part is anaplastic. Many of the cells are large, and have bizarre nuclei. Others are multinucleated. On cytological structure this tumour might be considered malignant, but in the part sectioned there is only superficial infiltration into the muscle, and this is important.



Showing stoma—Gluck's tube removed

FIG. 11.

The case is that of a woman on whom I operated nearly sixteen years ago, at the age of 59, and she is still alive. She was shown at this Section about two years ago, and there is no doubt that the reason why she has shown no signs of recurrence, in spite of the growth being classified as anaplastic, is the fact that infiltration into the muscle was at a very early stage, or that in this giant-celled type the histological appearance belies its malignancy.

This patient is rather unique inasmuch as she refused to undergo the plastic operation for the closure of the pharyngeal stoma. For sixteen years she has thrived and enjoyed solid food. She has taught herself to care for her Gluck's tube properly, and by this means she has perfect control of her swallowing and secretion of saliva (Fig. 11).

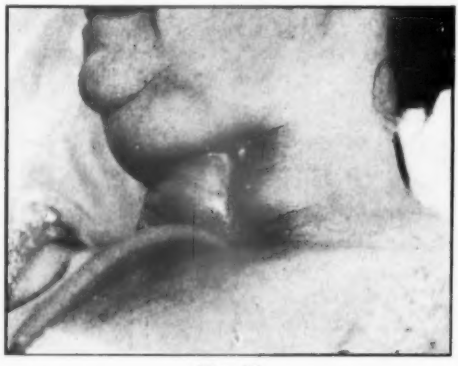


FIG. 12.

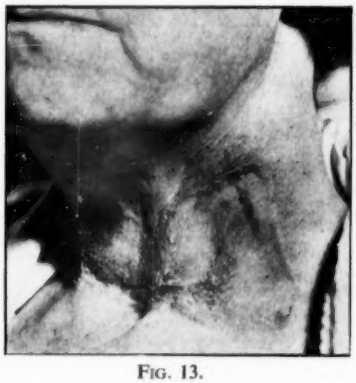


FIG. 13.

Pharyngo-laryngectomy and *transthyroid pharyngotomy*.—One or two points may be mentioned: Firstly, the difficulties encountered in a neck that has recently been irradiated when one has to decide to perform a transthyroid pharyngotomy for a recurrence. The trouble in these cases is confined mostly to the skin reaction (Fig. 12) with its reactionary œdema complicated by the persisting lymphatic stasis. When this occurs it is necessary to wait for months before one proceeds with the plastic operation for closing up the stoma. Even then great attention must be paid to the lower opening, as there is an extreme tendency for this to close up, reducing the lumen to 2 or 3 mm. This can happen although care has been taken at the first operation to cut the œsophagus obliquely. If doubt remains as to the fate of this narrowed lumen it is by far safer to remove the scarred lumen, and skin-graft the raw surface. This can be held in position either with a Souttar's tube or a polythene tube of the same shape and length. Fig. 13 shows the neck of the same patient after the plastic operation has been completed, and the skin lymphatic stasis having been absorbed completely.

Another difficulty encountered during a pharyngo-laryngectomy is the preservation

of the sternomastoid muscle where gland dissection of the neck has had to be carried out. This is particularly so when the large Wookey flap is used.

Fig. 14 is an example of what happens to the skin flap when its blood supply has been interfered with as the result of having to sacrifice too much sternomastoid. The tendency is for the upper attachment to slough off and roll back leaving a large pharyngostome. When this happens co-operation with a plastic surgeon is essential.

Fig. 15 shows the neck closed by means of a large pedicle flap raised from the chest, and in this case I am indebted to Mr. John Grocott for his kind and valuable help.

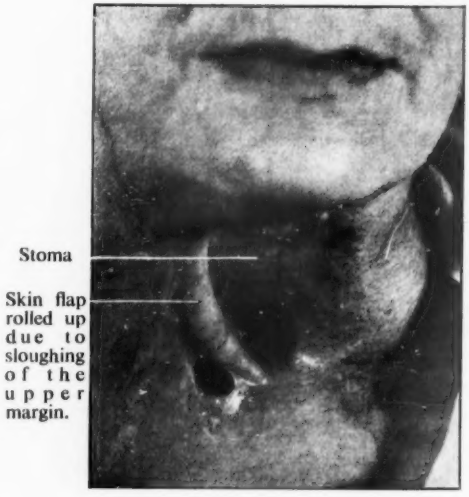


FIG. 14.



FIG. 15.—Pharyngostome closed by pedicle graft from chest wall.

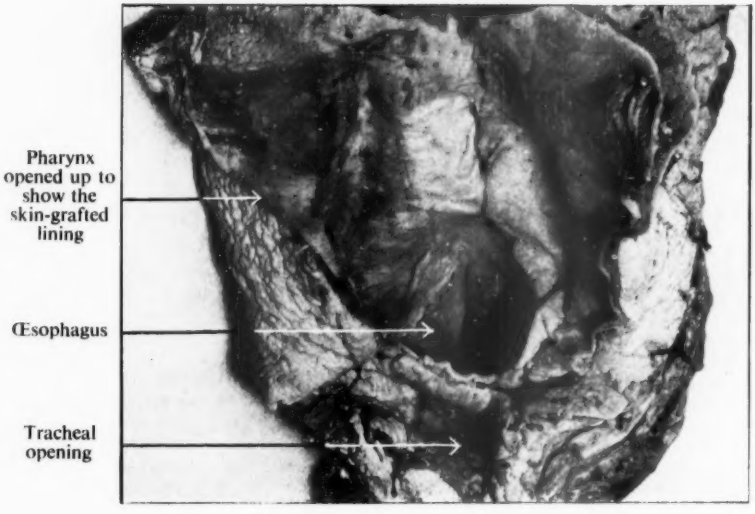


FIG. 16.—Post-mortem specimen. U-shaped flap opened up, showing skin-grafted pharynx and upper œsophagus.

The avoidance of multiple operations.—As Colledge points out in his Lettsomian Lectures it is sometimes necessary to proceed with as many as four stages before a lasting result can be achieved. There is nothing more distressing for the patient after a pharyngo-laryngectomy, than to find herself without a voice, and dribbling saliva through an open pharyngostome. In addition she has to be fed through a tube.

The primary closure of the pharyngostome will minimize this drastic change. This can be done if the original incision is of the "U"-shaped type as used for ordinary laryngectomy. When the lower pharynx and the larynx have been removed a Gluck's tube is inserted into position, and then surrounded by a stent mould. The whole stent now surrounding the Gluck's tube is removed and covered completely by a Thiersch graft removed from the thigh. The stent tube and skin-graft covering are now replaced into position and the "U"-shaped skin flap brought over the whole area and sutured into its original position—the lower end being carefully adjusted to the tracheal stump.

The external pressure.—Particular attention must be paid to the pressure that is applied on the surface of the skin flap and kept constant for at least seven days.

Two other steps are essential to the successful skin-grafting of a new pharynx : A gastrostomy and the provision of nasal suction to withdraw the pharyngeal secretions.

Fig. 16 shows a post-mortem specimen of a pharynx that was successfully grafted.

In conclusion one may emphasize that the only solution to this problem is early diagnosis and the recognition of the precancerous phase. If this, as a clinical entity, is accepted and recognized, one can decide on one of two things:

(1) Repeated œsophagoscopy as a method of routine follow-up when symptoms continue.

(2) When the dysphagia recurs with persisting mucosal changes, the vulnerable hypopharyngeal segment ought to be replaced by skin flap.

This in itself would be a great step to enable one to avoid the mutilating operation of pharyngo-laryngectomy which prevents the return of normal function as compared with a transthyroid pharyngotomy.

Finally the following figures show the low survival rate for extrinsic cancer as compared with intrinsic laryngeal cancer (Table V).

TABLE V

	Pharyngo-laryngectomy No. of cases	Post-op. deaths	Recurrence within 12 months	Recurrence within 5 years	Survived 5 years and more
Extrinsic cancer of the larynx	22	5	8	5	4 =18%
	Lateral pharyngotomy for postcricoid carcinoma and upper end of œsophagus	Post-op. deaths	Recurred within 12 months	Recurred within 5 years	Well after 5 years
	14	4	6	2	2 =14%
Intrinsic cancer of the larynx	Operations: Thyro-fissures, Radium fenestration, Total laryngectomy	46			Well 5 years and more 35 =76%

I would like to express my gratitude to my colleague, Mr. Emlyn Lewis, for his invaluable help and co-operation with the reconstruction and skin grafting of the pharynx following pharyngo-laryngectomy. Also to Professor Jethro Gough and members of his Pathological Department for their help and advice, and to Dr. Lewis Fanning, of the Statistical Department of the Welsh School of Medicine.

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V. E. Negus said that it was a matter of great regret that it had not been possible to obtain better results in this disease. One started by seeing Mr. Trotter at work and accepted anything he said as the right teaching; but confidence had been rather shaken as time went on. Mr. Negus would like to repeat what Mr. Owen had quoted him as saying in 1931 about the precancerous condition; he had not the slightest doubt about the relationship and Mr. Owen had confirmed this opinion in his Address. In 1938 he (Mr. Negus) was in the United States and in a discussion there on what was called the Plummer-Vinson syndrome, some surprise was expressed at the idea that this might be a precancerous condition. He did not feel that anyone could possibly be in any doubt; one saw cases too frequently.

The term "postcricoid" was misleading; most of the growths started at the mouth of the œsophagus on the upper surface of the cricopharyngeal fold, in the region affected by chronic inflammation. This was the lowest part of the pharynx and he would suggest that the proper term was "chronic hypopharyngitis". The condition commenced on the fold away from the larynx, on the posterior wall.

If treatment were carried out and failed to arrest the disease by dilatation or other means, and if it was thought that ulceration was going on, possibly with a little irregularity of the epithelium which, although not proved to be carcinomatous, seemed to have a probability of becoming malignant, the right thing to do appeared to be to remove that segment of the lower pharynx and upper œsophagus. It would be easy to separate the œsophagus from the back of the trachea and larynx with little chance of recurrence. The malignant changes would be on the posterior wall and reconstruction would give the patient the ability to swallow well, making the operation justifiable.

If malignant disease were established, one could see if there were any extension into the larynx or trachea by direct examination; if there were any infiltration it would be futile to leave the larynx in position. He had tried various conservative operations and had been very disappointed with results. It was a small matter whether one used the single large flap of Trotter or two shorter flaps. The latter appeared to be more reasonable and one was thus able to reconstruct the pharynx and œsophagus and restore swallowing. His experience had been that many, indeed the great majority, of these cases recurred. It was not possible to tell beforehand which case would and which would not recur.

There was a second possibility; if the top of the œsophagus and the lower end of the pharynx were removed, and reconstruction was carried out, the larynx was left lying against the raw front of the vertebral column. A case was referred to him recently where this had happened. The patient could not swallow because the skin tube was not complete; it was possible to complete it, but when the patient made an attempt to swallow everything he drank ran straight into the larynx. All his saliva overflowed throughout the day and night and the man was in a most miserable state. There was also double recurrent paralysis; he could not close the larynx and he could not pull it up against the base of the tongue because it was fixed. His distress was so great that the speaker removed the larynx and found in its lymphatic vessels some carcinomatous cells. It would have been better if the larynx had been removed earlier. He had seen the same condition occur in a woman who had had a very small growth irradiated. The growth was limited to one small patch on the posterior wall, but removed within a year. At operation it was possible to remove the segment and restore continuity by turning in two skin flaps. She had a left recurrent nerve paralysis because the skin flap lay over it, and the right recurrent nerve later became paralysed. She was in the same miserable state as the other patient; later she died from recurrences.

After these and other unfortunate experiences he felt that the limited operation was not justifiable. He did not believe that irradiation would cure these patients and there were therefore two alternatives: one, to do nothing, and the other to remove the lower part of the pharynx, the larynx and the top of the œsophagus. Pharyngo-laryngectomy could allow a patient to live happily; they could even learn œsophageal speech or have an artificial larynx, and he believed that it was the right operation in this dire disease.

The next point was with regard to restoring continuity. One had tried the ordinary procedure of turning in flaps, but this was tedious and was sometimes followed by stricture. Mr. Charles Rob and Mr. Bateman at St. Thomas's Hospital had tried a means of primary repair, at first using tantalum gauze and in later cases a plastic tube; discussing the problem with Professor Kilner, it was agreed that it was illogical to do any repair work without skin graft. About a week previously Mr. Negus operated on a patient who had a growth at the cricopharyngeal fold; it was extensive and therefore the larynx, part of the pharynx and the top of the œsophagus were removed, together with three rings of the trachea. The trachea was fixed to the skin and the top of the œsophagus was attached by some stitches to the prevertebral fascia. A plastic tube was inserted, reaching from the pharynx to the œsophagus with a skin graft around it; the skin flaps were closed over it. Irregular flaps were made, on the advice of Sir Archibald McIndoe, so that the line of incision did not coincide with the line of the skin graft. If one could carry out primary repair with safety, even if slight alteration were required later to assist healing, it would be of very great benefit both to surgeon and patient.

One other point was that he had been advised by McIndoe that it was best to leave the tube, covered with a skin graft, in position for six months. The patient could swallow through the tube, which was anchored with a piece of stainless steel wire.

In Mr. Negus' opinion the present position was that for carcinoma of the hypopharynx the proper procedure was pharyngo-laryngectomy with primary repair.

J. F. Simpson also thanked the President for his most interesting and excellent presentation of his subject matter. He had covered so much ground that his audience could only hope to speak on one or two points. He noticed that the President drew a distinction between the various forms of the growth, the hard infiltrating type and the softer fungating type. The speaker had recently had the misfortune to operate on a case of the latter type of growth which appeared very small when he looked at it through the pharyngoscope but when he removed the pharynx much of this was studded with pin-point deposits of growth so that the mucous membrane had a mammillated appearance. He thought this type in which there was quite a small primary ulceration and at a considerable distance multiple small deposits giving a mammillated appearance to the mucous membrane constituted a distinct clinical type. He took it he had wasted his time by operating on that throat.

Mr. Negus had clarified the question of whether to remove the larynx or not and his views fell into line with Mr. Lionel Colledge's teaching. There could be no doubt that if the growth had become attached to the back of the larynx the correct procedure was to remove the larynx and pharynx and not to risk leaving a small piece of neoplasm on the larynx.

The pictures shown at the meeting indicated that the removal of a larynx to-day was not nowadays such a gross disability. He noticed that Mr. Negus spoke of the "œsophageal" voice, he believed the speech therapists were now cultivating a "pharyngeal" form of voice.

Professor F. C. Ormerod congratulated the President on his very remarkable results. He, like others, had struggled with these extensive removals of the larynx and pharynx, which were tedious, required a number of operations and much care over long periods and the results were not always satisfactory. There was a tendency to recurrence on the mucous membrane side of the junction with the skin flaps, either above or below, and he felt that this was due to a submucous extension of the growth far beyond its visible or palpable limits.

He felt that there were still hopes that radiation would cure these growths. He had worked for more than twenty years with radium bombs, from 1 gramme up to 5 grammes and the results had been very poor. Now that 10-gramme units were available, more successful results were being achieved. In January 1948 two old ladies, over 70 years of age, were treated with the 10-gramme bomb, one for a postcricoid and one for pyriform fossa growth. Both were perfectly well to-day and swallowing normally. It was anticipated that similar results might be achieved with the new very high voltage X-ray apparatus.

R. R. Simpson supported Professor Ormerod in his plea that irradiation should not be altogether discarded. He was reminded of the earliest hypopharyngeal carcinoma on which Mr. Colledge operated. It was a growth about the size of one's little finger-nail. He had advised irradiation but he gave the patient the alternative of seeing Mr. Colledge who advised resection. It was carried out in Mr. Colledge's masterly fashion but the skin flap sloughed and the patient was sent back to the speaker until such time as repair could be made. Within two months the patient suddenly had a hæmoptysis and when his chest was X-rayed it was found that he had extensive secondaries all over the lungs.

On the other point of the incidence of hypopharyngeal carcinoma with anæmia and dysphagia, it had interested him very much for years. It was rather remarkable that there was such a wide variation in the published incidence. For instance, the President's figures at Cardiff were at

variance with Flett's of Derby, and both these sets of figures were in variance with the figures which he got in the East Yorkshire–Hull area which again were entirely at variance with Vinson's figures in America. Vinson wrote him at the end of 1939 to say that he never saw carcinoma and they still regarded the condition as hysterical manifestation although they did agree that mucosal change occurred which they thought was due to defective keratinization and probable riboflavin deficiency. In the European figures there was a wide divergence. The Swedish figures showed a much higher incidence than was seen in this country, the figures for the different countries gradually decreased until in the Mediterranean area they appeared not to see carcinoma. In the East one saw anæmia with dysphagia but he did not see any cases with carcinoma. Was this a geographical variation in one type of disease? It did occur in other diseases; were they dealing with some geographical variation of the precancerous phase?

H. V. Forster said he would join other members in their appreciation of the Presidential Address, and not having done any major operations to relieve this dismal affliction of the female hypopharynx he would praise the diligence and courage of those who had performed them.

He had not found in his experience that the syndrome of dysphagia with anæmia had been a regular precursor of postcricoid cancer, and from his reading imagined this was the opinion of some other observers.

He had seen for the first time in 1935 at the Finsen Institute in Copenhagen soft tissue radiographs demonstrating amelioration in this disease where improvements in insulation of the apparatus had made possible the use of higher voltages.

He would express the hope that having reflected the skin of the neck, and perhaps separated deeper tissues, short period massive doses of X-rays may be applicable to cancer of the hypopharynx.

The President, in reply, expressed appreciation for the kind things that had been said by Mr. Negus and others. He was grateful for the contributions made during the discussion. In his view the most important fact brought out was the agreement regarding the necessity of recognizing the precancerous phase in cases of chronic hypopharyngitis, with or without anæmia.

The replacing of the vulnerable segment with skin flap, during that phase, was not a difficult procedure, but one had to be very certain of the presence of this early phase before advising operative interference.

Mr. Negus's point regarding bilateral recurrent laryngeal nerve involvement was not a usual picture, but where it did occur it was, as a rule, caused by a recurrence of the growth. It need not take place as part of the operative technique, and the possibility should not act as a deterrent in dealing with cases of chronic hypopharyngitis. He was glad to hear that primary repair following pharyngo-laryngectomy was recognized as the reasonable thing to carry out.

Mr. J. F. Simpson's remark regarding his own case emphasized the importance of recognizing the mode of downward extension that is liable to take place. This sometimes could be palpated during operation, before the pharynx was opened. If in doubt as to whether one could get below the growth, then the case was best left alone and ought to be referred for deep therapy treatment.

Section of Dermatology

President—W. N. GOLDSMITH, M.D., F.R.C.P.

[*November* 17, 1949]

Chronic Papular Dystrophic Dermatosis with Nail Changes. ? Lichen Planus.—L. FORMAN, M.D., and H. HABER, M.D.

Mrs. A. B., aged 53.

First seen October 1946 with a twenty years' history. On both legs from the knees to the ankles there were many closely set dull red papules, some flat, others domed. The papules were discrete or confluent to form a line or a mesh; over the right ankle they formed a continuous plaque covered by a crust and superficially ulcerated. A few papules were found on the nape of the neck. There was some irritation.

All the toe-nails were thickened and brown, and two finger-nails were discoloured, opaque and thick, and pinched up from the nail bed. No fungus was found in the nails.

The legs have been protected by Unna's paste and after six months the condition showed regression, with atrophy. Many of the papules developed milium bodies as they faded; others showed subepidermal blisters. Small areas of atrophy corresponded with the individual papules which had involuted and recalled the atrophy of lichen planus or lichen sclerosis.

To-day, papules are seen over the left knee, and right shin and ankle, with atrophy of the skin.

The clinical diagnosis suggested that from time to time there has been lichen planus, prurigo nodularis and lichen amyloidosus. No amyloid was to be seen in the sections.

Dr. Haber presented slides to illustrate the peculiar histologic features. Several biopsies had been performed in the last three years. All showed different features.

First section: Atrophic epidermis, flattening of the epidermo-dermal junction, sclerotic papillary body with gaping blood vessels and lymphocytic infiltrations; the rest of the cutis apparently normal. Immediately under the epidermis was a typical milium the origin of which could not be traced.

Second section: Similar epidermo-dermal changes, but in addition there was a clear separation of the epidermis from the papillary body.

Third section: A fully developed subepidermal bulla has formed. The roof was provided by an atrophic epidermis, the base by a sclerotic papillary body. The bulla was clearly secondary to the atrophic changes. In addition there were several rete pegs left within the papillary body, as they were torn away by the separating bulla, a process similar to that seen in epidermolysis bullosa hereditaria. These remnants of rete pegs were the origin of milia, which were a conspicuous feature in the case.

Dr. Haber concluded that there was definite histological evidence of lichen planus atrophicus with superimposed bullous formations terminating in papules containing milia. The condition is chronic and has to be distinguished from lichen planus pemphigoides, which is an acute eruption.

Ulcers of Foot with Congenital Arteriovenous Communication of the Right Lower Limb.—L. FORMAN, M.D., and H. E. HOLLING, M.D.

J. C., female, aged 21.

At the age of 4 years a hot swelling was noticed on the dorsum of the right foot. An orthopædic surgeon stated at that time that there was no bony abnormality and encased her leg up to her knee in plaster, which the patient wore for some months. Within a year the swelling had disappeared, but ever since that time the foot has been noticed to be hot and to sweat more than the other foot. The patient suffers from chilblains in the winter on her left foot but not on the affected limb. For the same length of time the skin on the dorsum of the right foot has been pigmented brown. Although she wears the same size shoes, the patient has noticed that the dorsum of the right foot projects above her shoe more than the left one.

Fourteen months ago a scab appeared on the dorsum of the right foot and when the patient removed this a shallow ulcer was left which refused to heal. Two months later a second ulcer appeared and later a third ulcer at the base of the second toe and a fourth ulcer on the dorsum of the second toe. Various local treatments were tried without effect and local penicillin was followed by generalized urticaria.

In March 1949 she was admitted to hospital and all the ulcers healed with saline dressings. Soon after discharge two of the ulcers broke down again.



FIG. 1.

In September 1949 she was admitted to Guy's Hospital. On examination there was an area of bluish-brown discoloration and thickening of the skin on the dorsum of the right foot with an ulcer in the centre of the area and a second ulcer on the second right toe (Fig. 1). The ulcer was approximately 1½ in. long and ½ in. wide, with its greatest length in the long axis of the limb. The edges were thickened and a pyogenic membrane covered the floor of the ulcer. So bizarre was the appearance that at first the diagnosis of dermatitis artefacta was entertained. However, there was a marked difference in the temperature of the two feet. The right tibia was 1 in. longer than the left. The dorsalis pedis and anterior tibial arteries on the affected side were enlarged and the veins were slightly more prominent. On the sole of the foot there were two areas about the size of a penny, one under the metatarsal heads and one on the heel, markedly hotter than the rest of the foot and showing capillary pulsation on pressure. The blood pressure in the two lower limbs was the same—160/90. Apart from generalized dermographia, there were no other abnormalities.

Investigations.—Hb 76%; R.B.C. 3,800,000; W.B.C. 8,300—normal differential. Wassermann reaction and Kahn negative. Culture from ulcer—coliforms only. X-rays confirmed increase in length of tibia but showed no definite change in the size of the bones of the feet. There was no bony abnormality. Infra-red photographs showed slight increase in the veins of the right leg.

Dr. H. E. Holling: The important points in the diagnosis of this case of arteriovenous fistula were (*a*) the condition had been present since birth, or shortly after birth; (*b*) the ulcerated foot was warmer than the normal foot; (*c*) the right tibia was longer than the left; and (*d*) the veins of the right calf were dilated (though not varicose).

The right foot was found to be 5° C. warmer than the left, and the skin of the dorsum, ball and outer half of the heel of the right foot was 3° C. hotter than the skin around. (Right foot 31 to 34° C., left foot 26° C., room temperature 24° C.) This finding indicated that the blood flow to these areas was greatly increased. On the outer side of the right heel large skin capillary vessels could be seen with the naked eye. The blood flow to the right foot was measured by means of a plethysmograph and found to be 180 ml./minute whereas that to the left foot was only 10 ml./minute. Arterial blood (95% saturated with oxygen) was obtained from the dilated vein at the internal malleolus.

In my experience this case is unusual in not having varicose veins. The usual picture is of a patient of 20 to 30 years of age with varicose veins and malleolar ulcers. The diagnosis is sometimes made during injection for the varicose veins when it is found that blood withdrawn from the veins is of bright arterial colour.

In order to show the extent of the lesions it will be necessary to do an arteriogram in this case. Surgical removal of the fistulæ is likely to be difficult because the angiomatous tissue appears to be embedded in the deep tissues of the foot. If the ulceration becomes intractable we shall have to consider amputation, either of the foot or from below the knee.

It is strange that skin ulceration should be associated with apparently increased skin blood flow. I believe, however, that the actual skin blood flow is diminished because blood is being diverted through the fistula instead of passing through the overlying skin. The increased skin temperature, which usually denotes an increased skin blood flow, is the result of the increased blood flow in the fistulæ underlying the skin. We cannot put this supposition to the test because we have no direct way of measuring skin blood flow. In a comparable case of pulmonary arteriovenous fistulæ, however, the blood flow through both fistula and normal lung tissue could be measured. When this was done it was found that a large blood

flow through the fistula is associated with a diminished blood flow through the normal lung tissue.

Dr. R. E. Bowers: There is a fairly loud blowing murmur beneath the metatarsal arch at the site of the area of discoloured skin. I could hear no murmur over the heel but possibly one would be able to do so in a quieter room. The murmur might be of value in localizing the arteriovenous communication.

Purpura Annularis Telangiectodes (Arciform Type—Touraine).—BRIAN RUSSELL, M.D., and R. N. R. GRANT, M.B.

Miss S. L., aged 18.

History.—In December 1948 she noticed a non-itching discoloured patch on the inner side of the right thigh which gradually enlarged. She was first seen in June 1949 and the accompanying photographs show the progress of the lesion during the following four months. The lesion was flat and roughly annular, about 4 in. in diameter, the centre pigmented but not atrophic, the edge consisting of purpuric and telangiectatic elements (Fig. 1). The lesion gradually spread peripherally and cleared centrally, the edge breaking up into segments and almost disappearing after about eleven months (Fig. 2).



FIG. 1.—Condition on 21.6.49.



FIG. 2.—Condition on 4.10.49. (Biopsy scar at top on right.)

She now presents four more recent lesions on the thighs in discoid and annular form.

General health is good. She takes no drugs. The teeth are sound and the throat normal. The urine is normal. Wassermann and Kahn reactions are negative.

Histology.—The vessels of the superficial corium show capillary dilatation and some surrounding infiltration, mainly of round cells, with some polymorphonuclear cells. There is slight extravasation of red cells which show a little scatter. Hæmosiderin is not seen and the only pigment noted is the melanin in the basal layers of the skin and the melanophores, and this is not grossly increased.

Comment.—Touraine, in reviewing the capillary ectasias (*La Presse Médicale*, 1949, **65**, 934) points out the differences between this condition, of which he has seen 5 cases and collected others from the literature, and the Purpura Annularis Telangiectodes of Majocchi, in which the lesions are smaller, more numerous and leave hæmosiderin pigmentation and some atrophy. It occurs more often in the female than in the male in the proportion three to one, whereas Majocchi's disease is equally distributed between the sexes. In both diseases the majority of cases occur in young adults (under 40) but Majocchi's disease shows a higher incidence in the older age-groups. Touraine's illustrations correspond closely to the photographs shown of this case and to the present lesions, leaving little doubt that this patient is suffering from the condition which he calls Purpura Telangiectasique Arciforme.

Sarcoidosis following Injury.—R. D. SWEET, M.R.C.P.

A man, aged 32, was blown up by a mine in April 1945. The mine was of the wooden box type, filled with gun cotton, and buried in a field in loose soil. His left foot was blown off and he was heavily peppered with small particles mostly on the hands, face, chest and legs, and also in both eyes.

Foreign bodies were removed from both eyes and the sight was restored to Right 6/6, Left 6/5. There were many dark marks on the hands, especially the left, and also on his chest and both thighs, and over the whole of the face. These, however, caused no inconvenience and no swellings. He remained fit until January 1949, when, almost four years after the injuries, he noticed blurring of vision in the left eye and at about the same time a swelling by his left elbow. Soon afterwards many firm painless swellings appeared on the left hand, the face, legs, right hand and on both forearms. These increased in size until April 1949 when they became stationary. Vision in the left eye became progressively worse and he could see a white patch over the iris which continued to increase in size until by July the eye was quite blind.

Past history.—Nothing of note. No suggestion of tuberculosis at any time.

Present state.—Opacity in anterior chamber of left eye, apparently arising from the iris. Numerous small nodules scattered over face and eyelids, some obviously in relation to imbedded dark-coloured foreign bodies. *Left hand*: Diffuse firm, non-tender swellings along dorsa of fingers and on dorsum of hand. Many dark foreign bodies. *Forearms, right hand, both legs*: Widely scattered small flesh-coloured nodules. Enlarged rubbery glands in axillæ and sides of neck and epitrochlear regions. Liver and spleen not palpable. No other abnormal physical signs.

Investigations.—Mantoux positive 1/10,000. X-ray chest: Possibly some hilar gland enlargement. X-ray hands: Middle phalanx left fourth digit shows a localized area of translucency in the mid-shaft. E.S.R. 5 mm. in one hour.

Histology (Dr. I. W. Whimster).—(1) *Skin*: The dermis contains many discrete and confluent foci of tuberculoid granulation tissue in which are several areas of necrosis, many appearing to have arisen in the connective tissue between tubercles rather than inside them.

Scattered throughout the lesion, and to a lesser extent the adjacent skin, there are many variably sized polyhedral, doubly refractile, crystalline particles, a few of which are within giant cells. No acid-fast bacilli could be demonstrated in the five sections examined for them.

(2) *Lymphatic gland*: Most of the gland tissue is replaced by confluent and discrete foci of histiocytes with giant cells, lymphocytes and eosinophils. There are no areas of necrosis nor any doubly refractile particles in the sections examined.

Treatment.—He has been treated with calciferol, 1,200,000 units a week and streptomycin 1 gramme daily, and the lesion in the left eye has decreased in size, as have the scattered lesions on the face. His hands and the enlarged glands remain unchanged.

Comment.—The biopsy section of the skin shows doubly refractile particles in close association with giant cells. Yet, both clinically and histologically, the picture is like sarcoid or tuberculosis, especially the former in that there is no fibrous reaction. The section of the lymph gland is typical of sarcoidosis, and here there are no doubly refractile particles.

When silicates are introduced into the body, be it into the lungs, or within the peritoneum as talc on the surgeon's gloves, the reaction produced is intense fibrosis. If the regional glands become involved they become fibrotic and doubly refractile bodies are seen within them. The gland in my case shows no fibrosis.

Furthermore, this fibrotic reaction is more or less immediate. Walker (1948) and Mackey and Gibson (1948) report cases of intraperitoneal "siliceous granuloma", probably due to talc, occurring seven weeks and only thirteen days after operation.

Yet surely, except in the lungs, only certain people react to silicates. Innumerable abdomens have been contaminated with talc and many skins have been impregnated with debris and soil by explosions without developing sarcoid-like granulomata. Is it certain that in the peritoneum infection did not cause adhesions and that talc lying around was not phagocytosed by cells mobilized for another purpose?

Again, how can we explain the immediate fibrous peritoneal response and the long-delayed tuberculoid skin response, so well shown in my case where almost four years with perfect sight went by, before a tumour developed in his uveal tract?

There is a curious association between tuberculosis and trauma. Tuberculosis colliquativa not uncommonly occurs at the site of some previous minor injury and trauma sometimes seems to determine the site of tuberculous infections of bone, in patients apparently free from active tuberculosis. Tuberculosis usually complicates silicosis of the lungs and Fletcher (1948) suggested that progressive massive fibrosis only occurs because of the superadded tuberculous infection.

If it is agreed that sarcoidosis is a manifestation of tuberculosis, it does seem possible to regard this case of mine and others similar to it that we have seen at this Section recently in this way:—

Trauma has occurred and foreign bodies are present. Tuberculous infection has occurred in the past. The patient's resistance and reactivity fluctuate and at some stage he reaches a state when the presence of the foreign body tips the scales against him locally and a tuberculoid focus results.

Perhaps it is only at this stage that the giant cell ingests the doubly refractile particle! The important thing is that the patient's response is a pathological and not a normal one to the presence of foreign bodies.

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Tuberculous or Silicotic Granulomata.—G. C. WELLS, M.B., and W. N. GOLDSMITH, M.D.

Mrs. A. D., aged 32.

History.—Six months ago lumps appeared in scars that had been present for many years.

In 1937 she had a cycle accident on a gravel road causing multiple lacerations which healed with scarring.

In 1939 a tuberculous gland of the left side of the neck broke down (tubercle bacilli were recovered from the pus). After surgical drainage the wound healed soundly.

Her general health has been good.

On examination (July 1949).—On the left side of the face, left shoulder and right elbow there were raised nodular lesions extending out from the edges of old scars, the nodules having the "apple jelly" colour characteristic of lupus vulgaris. On the back of the right hand and wrist were several raised, rather more lichenoid granulomata, again in the substance of old scars. Lesions were noted only in the scars from the old cycle accident, not in other scars nor in unscarred areas (Fig. 1). There was discrete, rubbery enlargement of the right epitrochlear gland.



FIG. 1.—Lesions of lupus vulgaris in old scars.

Investigations.—Radiograph of the chest in July 1949 showed marked enlargement of the hilar glands and a paratracheal gland. Mantoux reaction was positive (1 : 1,000). Biopsies were made from three of the skin lesions and the right epitrochlear gland was removed.

Histology.—In the skin sections there are foci of tuberculous granulation tissue at various levels in the dermis. There is rather more central necrosis than is commonly seen in lupus vulgaris. In one section there are some minute doubly refractile particles in and among

the histiocytes but silica is not convincingly demonstrated. The lymph gland on the other hand shows replacement of its normal structures by numerous neatly arranged islands of epithelioid cells exactly in the manner of sarcoid.

Fresh material was taken from one skin biopsy and from the lymph gland, and with this Dr. Wetherley-Mein inoculated culture media and animals. No growth of tubercle bacilli was, however, demonstrable.

Progress.—While under observation in July and August 1949, the patient developed erythema nodosum of the legs, which subsided in six weeks.

In October 1949 radiograph of the chest showed the hilar glands to be no longer enlarged.

While in hospital recently there has been no fever or cough, blood findings have been normal and general health has been satisfactory.

Calciferol therapy was started in October and there has been a striking response. After just over 5,000,000 units of vitamin D, the lesions have flattened out and there is hardly any trace of granuloma.

Comment.—Of particular interest in this case is the recent appearance of multiple lupus vulgaris lesions in scars that had been present for twelve years, only those scars which resulted from the road accident being affected. A scar on one finger following an accident with a printing machine when she was 16 years old shows tattooing from inclusion of black ink, but no lupus. Neither has lupus appeared in the surgical scar on the neck.

It seems likely that there has been a recent dissemination of tubercle bacilli by the blood stream in a subject whose resistance is good; and a proliferative reaction has only taken place at favourable sites in the skin, namely those scars that probably contain some silica inclusions. Kettle (1932, *J. Path. Bact.*, **35**, 395) demonstrated that in mice the tissue reaction to silica suspensions injected subcutaneously was distinct from the reactions provoked by "inert" dusts, and that the silica reaction favoured the accumulation or multiplication of tubercle bacilli, after living bacilli had been injected into the circulation.

In this case a changing reaction to tuberculosis is suggested by the transient hilar gland enlargement and erythema nodosum. The sarcoid reaction in the lymph gland close to the lupus reaction in the skin is also of interest.

Dr. Sommerville: In Dr. Sweet's case there is no doubt about the crystalline material in the section and I thought there was some evidence, no matter how slight, of some highly refractile material in the other section. Admittedly in tuberculoma silicoticum there should be a sarcoidosis reaction and we think it might be related to tuberculosis. The reaction of Kveim can be produced by several types of materials injected and yet give a specific tissue response. I do think that this type of lesion, which is of the lupoid form rather than the sarcoid type, is a specific tissue response occurring in a peculiar subject probably of the tuberculous type.

Hidradenitis Suppurativa (Apocrine Acne).—W. N. GOLDSMITH, M.D.

W. H., man, aged 28, admitted to the Hospital for Tropical Diseases on 1.11.49, under Professor Hamilton Fairley.

History.—He was born in England, went to India at the age of 3, and remained there until August 1948, when he returned to England. While abroad he had severe *enteric fever* in 1935 and *pneumonia* in 1937.

In 1936 a *perineal abscess* formed, which ruptured spontaneously and healed, and one month later a similar abscess formed on the right side of the scrotum. Treatment in hospital in India was not effective, and lesions continued to recur. Later they spread on to the inside of the thighs, and in 1942 on to the buttocks, and in 1945 into the axillæ.

The general evolution is for a lesion to form pus, drain spontaneously, and, instead of completely healing, to track under the skin and break out at a distance as a similar lesion.

The condition has extended without the patient's seeking any medical advice. But since the beginning of this year, he has been treated at Kingston and Farnham Hospitals with sulphonamides, penicillin, zinc peroxide, and calciferol. The tentative diagnosis was acne conglobata.

Present State.

General condition.—He feels well; no constitutional disturbance, except when sepsis becomes excessive and he gets some fever. Walking is somewhat impeded. Weight: 12 st. 7 lb.; lost 11 lb. since last May. Appetite good.

Physical examination.—Carious teeth; some enlargement of axillary and inguinal glands; no enlargement of liver or spleen; no albuminuria, or other signs of amyloid degeneration.

Skin—Right axilla: Healed lesions with some scarring, contraction, and comedo formation. Left axilla: Similar, but some of the lesions are active.

Buttocks, perineum, and inner, upper aspect of thighs: Large areas of indurated, scarred, bluish skin. The area is riddled with sinuses discharging green, creamy pus, and pressure on any one part causes pus to ooze at a distance.

Investigations.—Blood-count: R.B.C. 3·89 millions; Hb 80%; C.I. 1·03; W.B.C. 12,200 (P. 67, L. 25, M. 4, E. 4%).

Fæces: Semi-formed, normal colour. No pathogenic ova or protozoa, and no cellular exudate.

Urine: No sugar or albumin. Deposit normal.

W.R. negative.

Pus: Mixed bacterial flora of Gram-positive and Gram-negative cocci and bacilli. No mycelium found. No acid-fast organisms. Culture: Sparse growth of *C. xerosis*.

Mycological investigation.—No fungus seen in smear or grown after ten days' incubation.

Since admission, purulent discharge has increased in association with fever, rising nightly to 99·6°–100·4° F. Treatment resumed with penicillin and sulphonamide, with much improvement.

Points in favour of the diagnosis are the distribution, chronicity, and perhaps the co-existence of acne over the scapular region.

Special points of interest are the very slight constitutional disturbance and painlessness.

Hidradenitis suppurativa is similar to other acnes in that it is a suppurative condition of the hair follicles, very chronic, producing in some cases a lot of pus but with remarkably little local or constitutional disturbance. It is the distribution and the histological appearances that make us associate it with the apocrine glands and distinguish it from acne vulgaris and acne conglobata. The bacteriology appears to be as negative in this as in the other two kinds of acne.

With regard to endocrinology we feel fairly convinced that the endocrines play a considerable role in acne vulgaris; in acne conglobata it is not quite so clear, but it mainly affects adult men. Finally, in this apocrine acne there does not seem to be any endocrine upset and the sex incidence is about equal.

Mr. Naunton Morgan has suggested that the best plan will be to lay open the sinuses, region by region, and allow them to heal up from the bottom.

I have never seen such an extensive case. When the condition is limited to the axillæ we usually treat it with X-rays; I do not think this man has ever had X-rays. Should we resort to surgery alone, X-rays alone, or a combination of the two?

Dr. H. J. Wallace: In a similar patient at St. Thomas's Hospital, resolution was secured only by having all the sinuses laid open, the whole treatment lasting for about a year. One axilla was similarly treated without any benefit, but the inflammation in both axillæ appeared to respond to short-wave diathermy and antiseptic compresses.

Wing-Commander H. E. Bellringer: I saw a similar case aged about 45 who had had the condition since he was 20.

He had been bed-bound for the last ten years and had been treated about twelve years earlier by having the sinuses in the axillæ laid open. When I saw him they were completely healed, there was a mass of scars but no suppuration or sinus. There were tremendous tunnellings on the buttocks, groins and running through the perineum, the whole area looked like a rabbit warren.

On Dr. Barber's suggestion I put him on to pregnanediol and he seemed to improve gradually. We decided to lay open as many sinuses as possible and the man made a slow but uneventful recovery.

I saw him recently, some eleven months after the operation; he is now ambulant although he is not yet ready for work. There is no suppuration or local discomfort. The œstrogen therapy was stopped about three months ago, he never suffered any secondary effects from that or any toxic symptoms. I cannot say what part it played in his cure, probably very little because there was radical cure in the axillæ.

Dr. D. S. Wilkinson: I was looking after this patient some months ago. Every known antibiotic and antiseptic was tried and the result was the same as we have just heard described. There was slow improvement, then a relapse or a gradual slipping back. He has had œstrogen therapy for a period without any effect, and it does seem that surgery is the only thing which can help him.

Dr. G. B. Dowling: One surgical procedure has not been mentioned so far, namely, excision and skin grafting. An intractable hidradenitis of the left axilla in a young woman who was under my observation a few years ago was so treated with excellent result. The other axilla which was mildly affected cleared up spontaneously shortly after the operation.

Dr. Hugh Gordon: I think that a combination of surgery and X-rays should be tried in this case. The preliminary surgical measures would consist of a thorough "saucerization" of all the lesions, thoroughly exposing all the tracks, followed by applications of pure carbolic acid. The optimum dosage of X-ray is a very difficult one to decide. My own inclination would be a comparatively high dose for a fairly short time; for instance 250 r every five days for a total of four doses. Possibly the whole area need not be irradiated, but the dose limited to the worst areas of granulation.

Dr. L. Forman: I showed a case at the Section with the diagnosis of acne conglobata at the meetings of March and December 1947. He showed similar, but much more extensive involvement of axillæ, peri-anal skin and buttocks, with ramifying abscesses healing with epithelial bridges.

He had received X-ray therapy and was operated on on two occasions but relapsed and remained in hospital for long periods. Besides the offensive smell he developed a severe anæmia and loss of weight and it was feared that he would develop amyloid disease.

An implant of 300 mg. of stilbœstrol led to definite improvement.

Dr. Dowling: The case about which Dr. Forman has spoken ultimately came under my care having relapsed completely. The very severe acne however has again been brought under control by stilbœstrol 5 mg. daily.

The President: There is a close relationship between this apocrine acne, acne vulgaris and acne conglobata, but they are not identical. This man has mild acne vulgaris over the scapular region.

Dr. Dowling: Is there not a series of cases comprising acne conglobata, hidradenitis axillaris of the type now under discussion, severe cystic acne of the face and neck, and perifolliculitis abscedens et suffodiens capitis having in common the tendency to develop abscesses, sinuses, tunnels, scars, &c., and perhaps linked by some common ætiological factor?

? Parapsoriasis.—CLARA M. WARREN, M.R.C.S., L.R.C.P.

Jill D., aged 16.

The mother first noticed pink patches on the trunk when the girl was 7. They were more pronounced in the winter months, and did not improve after tonsillectomy.

When I first saw her at the age of 10 years 6 months (in 1945) there were brownish papules scattered over the abdomen, back and chest. These did not fade completely on pressure and appeared to be a form of pigmented urticaria. Dermographism could be elicited. Her general health and development were normal. Some improvement occurred after general ultraviolet-light therapy.

I did not see her again for three years (1948). She then showed thickened erythematous areas over the trunk, with smaller discrete patches resembling pityriasis rosea. The plaques showed some brownish staining but there were no isolated pigmented urticaria papules. There was some evidence of ulceration with scab formation, but no pruritus.

A year later, at 16, there are extensive areas of telangiectasis and brownish pigmentation, affecting abdomen, chest and back, and extending symmetrically down on to the thighs. Papular urticaria has been present on the thighs and legs. The dryness of the skin has developed within the last few weeks. Monthly periods have been present for six months. Section of a recent lesion does not show mast cells.

Dr. Warren: I did consider the diagnosis of parapsoriasis and, following Dr. Barber's suggestion that cases responded to calciferol, I tried it for four or five months and it has had no effect on the lesions. I think many members thought of the suggestion of parapsoriasis and also of some abnormal form of reticulosis, or some other blood disorder, but nobody was very definite.

The President: It was parapsoriasis which first suggested itself to me. Some of the lesions did seem infiltrated.

POSTSCRIPT.—March 1950. Blood count shows no abnormality—C. M. W.

Keloid Associated with Acne in a Young Girl.—D. L. REES, M.B., for H. J. WALLACE, M.R.C.P.

Miss P. R., aged 27.

In November 1945 she was treated for a moderately severe cystic acne involving the face, chest and shoulders, first with routine local therapy and later with superficial X-rays (5 doses 100 r).

At that time small, firm lesions were scattered over the shoulders and chest which were thought to be inspissated sebaceous cysts with ? keloid change.

The acne improved, but in January 1946 two biopsies of the nodules on each shoulder showed them to be fibromata and they continued to increase in size.

The biopsy scars rapidly became keloidal, showing that the "keloidal tendency" was present.

She was referred to the plastic surgeon, who advised X-ray therapy and a course of short distance "Chaoul" therapy was tried, but, apart from slightly softening the lesions, no effect was produced. A total dose of 2,500 r, in 5 single treatments of 500 r, was used.

The lesions have remained unaffected by any form of treatment and appear to be quiescent.

Our main interest in showing this case is for prognosis and treatment.

The patient had the advantage of treatment at an early stage, when the lesions were still soft and vascular and the radiologist expected a good result.

Levitt, W. M., and Gillies, H. (1942, *Lancet* (i), 440), state that the response of keloids to X-ray therapy or a combination of X-rays with surgery is excellent in the early lesions, and this view appears to pervade the literature, especially the radiological literature, on the subject.

Several workers have suggested surgery followed by X-rays, which will have their maximal effect when the keloid tends to recur after excision, that is, from the 7th to 10th day. Some dermatologists are of opinion that it is exceptional for good results to be obtained in such cases, especially in acne keloid. The end-results may be worse than before treatment, as the keloid may be larger. One concludes that an extremely guarded prognosis should be given in these cases.

Dr. Dowling: I believe the optimistic forecast so often given in these cases to be on the whole misleading. On three occasions I have advised excision followed by radium therapy applied for the first time on the day of the operation. In each case the result has been a considerably larger keloid after the operation than before it.

Dr. Hugh Gordon: I certainly think that in this type of keloid which is long-standing, hard and resistant the best result is obtained by a combination of surgery and X-rays. The simplest procedure is excision and an X-ray exposure to the scar immediately after the operation whilst the stitches are still in situ, the optimum dose being in the nature of 800 r, the field, of course, being strictly leaded off. A more elaborate procedure, which undoubtedly gives excellent results, is for the surgeon to mark out his site of operation which is given a dose of 500 r, again strictly localized. At the end of five to six days the incision is made through the resulting erythema. A further dose of 500 r is given five to six days after the operation with the stitches in or out. This method obviously is not so simple and more time consuming.

Dr. I. Martin-Scott: I wonder why X-ray is given *before* surgical removal of the keloid. I recently had a case and went into the literature and eventually decided to remove the lesion, and Dr. Hilton of University College Hospital gave X-ray treatment (as if the keloid were still there) the week after. We considered the advantage of X-rays *after* operation was to retard the action of the fibroblasts. Why should X-rays be given *before* operation as well?

Dr. Hugh Gordon: I have never understood the rationale for the *pre-operative* X-ray, and personally have always used the alternative method.

Localized Panatrophy.—F. Ray Bettley, F.R.C.P.

A boy, aged 12.

Red areas appeared on the left buttock in September 1947, and later on the back of the thigh, which by March 1948 had become brown and shrunken. His mother says that his gait is affected and that he wears down the heel of his left shoe very quickly.

Previous history not relevant; no other complaints.

On examination.—Most of the left buttock is shrunken, subcutaneous fat having completely disappeared; there is also some loss of muscle substance. The skin over this area is irregularly pigmented and slightly atrophic, but there is no telangiectasia or redness. The skin is freely mobile over the subjacent tissues. On the back of the left thigh are two sunken areas about 3 inches across, and on the left calf two further areas; on the back of the right thigh is one sunken area. These areas are ill-defined and appear to result from a loss of subcutaneous tissue; they are not sharply punched out and the skin itself appears normal. There is objective weakness of the muscles of the left buttock.

Electrical reactions of these muscles normal. No demonstrable change in sensory or motor nerve function.

General examination normal. Blood chlorides normal. Creatinine excretion (three consecutive days) 877 mg., 734 mg., 766 mg. (normal 500 – 750 mg.). Creatine excretion 280 mg., 276 mg., 374 mg. (normal 0–200 mg.).

Histology.—Skin: The basal layer of the epidermis is pigmented. Slight lymphocytic perivascular infiltration. Fatty subcutaneous tissue absent.

Muscle: Muscle fibres are irregularly atrophic and show areas of coagulative necrosis. There is a patchy lymphocytic infiltration between the fibres.

Comment.—I have been able to find 3 other cases of similar although not quite the same sort. I was prompted to bring the patient here because of a similar case which Dr. Mitchell-Heggs and Dr. Borrie (1949) showed a year ago. Their patient was a woman who presented patches of atrophy and pigmentation; atrophy of the skin without sclerosis, and the vessels deep in the dermis and subcutis showing through the atrophic skin. There was no muscular change. There are those two differences between that case and mine, namely atrophy of the skin and no muscular change.

More like the present one was the case, the name of which I have borrowed for this patient, which was shown originally by Sir William Gowers in 1903 at the Clinical Society of London and followed up in 1939 by Barnes. That case was referred to as morphœic, intending, I think, to indicate a sharply outlined area rather than sclerosis.

Dr. Barnes kindly came and saw this boy and drew a contrast between him and his original cases and Gowers' case. In Barnes' original case, as in Mitchell-Heggs' case, there were areas of atrophic, thin, wrinkled skin with the veins showing through, again with no fibrosis; but there was degeneration and wasting of the muscle underneath the patch. Another point of distinction was the absence of pigmentation in Gowers' and Barnes' cases.

We now have three different pictures and the fourth is provided by a case of Dr. Barber's which was shown in this Section in 1932—a case of scleroderma or morphœa with atrophy of the subcutaneous tissue and muscle. I think it is clear that in that case there was a definite scleroderma, namely skin bound down to the subcutaneous tissue, but in addition to the morphœa there was a loss of subcutaneous tissue and muscle.

I present this case, therefore, as one which I have not been able to link up exactly with any of the previous cases. All show to a greater or less degree atrophy starting in the subcutaneous tissue with or without atrophy of the skin above or of the muscle beneath.

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Dr. Haber: This case was under the care of Dr. Jenner several years ago. A biopsy was performed at that time and my histologic diagnosis was scleroderma.

Dr. Dowling: I suggest that this may be a case of morphœa involving the subcutaneous tissue. Similar underlying muscle atrophy in morphœa of the ordinary more superficial type is not very rare.

Psoriasis Vulgaris et Linearis.—BETHEL SOLOMONS, Jr., M.D.

Miss E. L., aged 22.

The patient states that she has had psoriasis since the age of 4, and that the linear lesion was also present then.

One brother suffers with psoriasis.

She lost her right eye when 7, due to trauma.

Examination.—General systemic examination normal. She has psoriasis of the scalp, forehead, nails of fingers and toes, and the elbow.

The linear lesion on the right leg consists of keratotic masses which stretch from a site a little medial to the fibular head, to the middle of the big toe, in an oblique line crossing near the middle of the ankle-joint. The lesion lies upon a slightly erythematous base. It scales readily. On the big toe is a well-marked punctate keratosis. W.R. and Kahn negative. Blood-count normal.

Treatment.—There has been a fair response to tar and salicylic acid.

Histology of the linear lesion was done four years ago at the Royal Staffordshire Infirmary, and was stated to be psoriasis.

Comment.—This case is presented because of the renewed interest in linear psoriasis. It may straightaway be said that many consider it to be a linear nævus.

A recent article by Auken (1949), from Lomholt's clinic, records a case extremely similar to this one in a girl aged 9. Cases of true linear psoriasis are also reported on by Stangenberg (1922), Thibièrge (1893) and Wagner (1921); Kreibich (1917) discussed its nævoid relationships. Jadassohn and Darier do not write of it.

It is of interest that in this case the lesion follows faithfully the course of the superficial peroneal nerve, and thereby fits one of the tenets of Montgomery's essentials for a linear dermatosis, of which he wrote in 1901, and which are still unaltered.

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Dr. Bettley: I found it difficult to accept the linear lesion as psoriasis. I thought it was a hyperkeratotic nævus. I noticed that there was follicular plugging.

Dr. Sommerville: I looked upon it as a nævus unius lateris type of lesion and possibly the psoriasis developed on the traumatized skin of the nævus.

Dr. Sweet: She said that the psoriasis waxed and waned over the years whereas the lesion on the leg remained exactly the same, which tends to separate it from psoriasis.

Dr. Solomons: I think the latter may be a case of psoriasis superimposed on a linear nævus, but we are going to do another biopsy, if possible, and perhaps we could let you know the result. I would like to call to mind the recent writings of American authors who state that in many of their cases of clinically atypical psoriasis, biopsy is necessary for diagnosis.

The following cases were also shown :

Virilism with ? Ovarian Tumour.—Dr. L. FORMAN and Dr. W. H. MERIVALE.

Colloid Milium.—Dr. ALAN LYELL (for Dr. C. H. WHITTLE).

Eosinophilic Granuloma of the Skin.—Dr. P. FORBES BORRIE.

(These cases may be published later in the *British Journal of Dermatology*.)

Section of Anæsthetics

President—GEOFFREY ORGANE, M.D., F.F.A. R.C.S.

[*November* 4, 1949]

Change and Progress in Anæsthesia

PRESIDENT'S ADDRESS

By GEOFFREY ORGANE, M.D., F.F.A. R.C.S.

LOOKING back on the practice of anæsthetics before the last war, one realizes that there have been very considerable changes, changes as remarkable, probably, as in the previous twenty years. I wonder, sometimes, whether the rate of change we see around us is not too fast for most of us; I wonder where we are going and to what extent our journey represents progress.

The early anæsthetists devoted much of their time to work in the operating theatre. They were responsible for the formulation of anæsthetic techniques, for the development of many types of apparatus and for the investigation of a number of possible anæsthetic agents. Yet some, like Snow, found time to continue their researches into other branches of medicine; others conducted busy general practices. To-day there is a fast-growing tendency among anæsthetists to accept the confinement of their activities solely to the administration of anæsthetics. The specialist in a narrow field has, necessarily, a narrow outlook; the more he learns about, say, anæsthetics, the more he is apt to forget about general medicine. And this limitation is not at all necessary to the efficient practice of his specialty. In fact, a wide knowledge of general medicine is essential to the proper care of his patient by the anæsthetist.

It must be admitted, of course, that anæsthetic techniques have become much more complicated in recent years, and that a protracted period of training under supervision is essential if he is to become expert in administration. From the open mask and the Clover, with their rather limited range of possibilities, we have progressed to anæsthetic machines, streamlined and chrome-plated or stove-enamelled in pastel hues, whose powers of destruction in the hands of the half-instructed are as considerable as their powers for good when properly handled. We must be experts in intravenous, intrasternal, spinal, epidural and local anæsthesia: we must be laryngologists, tracheologists and bronchologists, and we must have something of the miraculous powers of guardian angels if we are to protect our patients against the onslaughts of some of the more radical surgeons.

To this extent the general practitioner is handicapped, that he cannot hope to master these technicalities by himself. To take one example, that of anæsthesia for intrathoracic operations: the recent developments in surgery have been made possible by the advances in anæsthesia; but these advances are not the result of one man's work, nor could they be: they are the result of the combined experience of many men over a long period. The relative isolation of general practice makes it difficult to keep up with the advancing tide of common experience, but I see no reason why, *if he is already fully trained*, he should not be able to keep himself up to date.

Let us assume, however, that we are to become anæsthetists, debarred from practising any other branch of medicine. We cannot be expected to spend the whole of our working time in the operating theatre. It would be as unreasonable as to expect surgeons to subdivide themselves into clinical and operating. We must have other interests to occupy a part of our time.

Logically, these interests should extend from the duties we undertake in the operating theatre. Our medico-legal colleagues hold that we are responsible, in law, for the pre-operative assessment of the patient's general condition and fitness for operation, for the selection of the appropriate premedication, for the choice of anæsthetic agent and technique, and for the care of the patient's health during the operation and during the immediate post-operative period, until recovery from the anæsthetic can be said to be complete. That is our duty—and our right; but we must be reasonable. Good surgery depends on good team work, which cannot exist without mutual confidence and respect. A team cannot be built from a number of individuals, however brilliant, who insist on pulling in opposite directions. We can best establish our position in the surgical team, not by an arrogant insistence on our rights, nor by extolling our virtues but, in the first instance, by demonstrating our ability to give a good anæsthetic, which, we are sometimes inclined to forget, is the prime reason for our existence. The rest will follow: most surgeons will tell you that they are only too happy to be able to leave everything to the anæsthetist, so that they may concentrate on the operation; but this implies an anæsthetic so unobtrusively good that the surgeon can forget about it.

Pre-operative Examination and Preparation of Patients

It still happens that the surgeon will call upon a physician, in a doubtful case, to decide upon the patient's fitness for operation. It can be very irritating to be told, the night before, that a patient has been seen by the physician, who has pronounced him "fit for a general anæsthetic". Such a vague opinion is of no value to us, and can absolve us of none of our legal responsibility to the patient. Fit for what general anæsthetic and, more important, by what anæsthetist? On the other hand, there are many cases in which we should be glad to have the advice of someone more expert than ourselves. The physician can best help us by recording his findings, and his interpretations thereof, which can guide us in our choice of anæsthetic agent and technique. Ideally, the physician, surgeon and anæsthetist will meet in consultation on any doubtful case, to discuss the problems involved. This practice already obtains in some centres and I have no doubt that it will be more generally adopted. Such discussions can do us anæsthetists nothing but good—and dare I suggest that the benefit could be mutual?

For many relatively trivial procedures the pre-operative condition of the patient is not of great importance; provided, always, that we treat him to the best of our knowledge and ability. It is often difficult for us to visit our patients beforehand, particularly when we first hear of their existence late in the evening before operation, and we often leave the pre-operative examination to a junior house surgeon or house anæsthetist. While this is far from ideal, it is generally adequate; but what are we to do when we are confronted with a patient who, we discover, has certain complications which we know are likely to reduce his chances of recovery from a major operation? With the present shortage of surgical beds, we may be reluctant to insist on the postponement of operation that we know is right. We believe that dirty teeth increase the chances of post-operative chest complications; we know that these are at least five times more common in heavy smokers than in non-smokers; we know that the chronic bronchitic should be kept under observation to ensure that he is at his best when he comes up for operation; we know that many patients with heart disease will benefit from a period of rest in bed, perhaps with digitalization; we know that immediate pre-operative transfusion is not adequate treatment for chronic anæmia with its accompanying myocardial changes.

The logical solution to this problem, as is often the case, has been reached simultaneously in more than one part of the world. While many of us have toyed with the idea, the Pre-operative Out-patient Clinic has been established. Mendez Peñate has one in Cuba; there is another in Southend [1].

There is nothing extravagant in this suggestion which, I believe, can do nothing but good. The patient could be examined at leisure; any necessary biochemical, pathological or radiological investigations could be completed, dental toilet could be undertaken, difficult cases or diabetics could be referred to the physician; the heavy smoker or the alcoholic could be frightened, at least into a reduction of his consumption, in time for real benefit to be gained. Where a period of rest in bed was considered desirable, this could be undertaken either in the patient's home or in a convalescent home—an institution much better adapted to pre-operative than to post-operative care. On admission of the patient to hospital, the anæsthetist in charge of the case would have access to the out-patient notes and would be advised which of his patients he should, himself, visit before operation.

Such an arrangement would seem to cover most deficiencies with the least inconvenience to the anæsthetist and with considerable advantage to a hospital that has to fit an appalling number of urgent cases into a totally inadequate complement of surgical beds.

Resuscitation and Oxygen Therapy

The anæsthetist is no longer the chloroformist but the man who keeps the patient alive in the operating theatre. This change in the conception of his duties began many more than ten years ago but it is only recently that it has been generally recognized. With the widespread adoption of the practice of keeping detailed records of the progress of the patient in major operations, the anæsthetist has become better able to interpret his findings —though we still find many reactions that pass our comprehension. I have no doubt that, as things are, the anæsthetist is the best placed in the operating theatre to decide upon and to supervise resuscitative measures.

As the anæsthetist is the resuscitation officer in the operating theatre, he could, usefully, become the resuscitation officer to the hospital as a whole with overall clinical charge of blood transfusion and all forms of intravenous therapy. This is not to suggest that the anæsthetist is, *ipso facto*, qualified to become resuscitation officer. Most of us have a fair working knowledge of the subject but our theoretical background is often woefully inadequate. Our training in these matters falls a long way behind that provided in many American and Canadian centres. The resuscitation officer should be as fully informed as any of his medical and surgical colleagues on all aspects of his work, if he is to be of real value to them. The task is beset with pitfalls and would require the closest and most tactful co-operation with physicians, surgeons and pathologists.

The anæsthetist who is also the resuscitation officer would include among his duties the supervision of oxygen therapy and the maintenance of apparatus. The need for such supervision will become apparent on inspection of the wards of any of our great teaching hospitals. The anæsthetist is the only member of the staff who is likely to be thoroughly familiar with the workings of the apparatus; from his duties in the theatre he understands the control of airway from the lips to the bronchioles and he is, or should be, an authority on all forms of artificial respiration.

I am convinced that we shall have to establish recovery beds where patients can be tended by experienced nursing staff in the early post-operative period, and I am also convinced that such beds are best placed in the charge of the anæsthetist. We are all aware of the dangers attendant upon the return of the patient, supervised by a theatre porter and a probationer nurse, to a ward where the harassed and overworked nursing staff, towards the end of a long operating list, have to combine their supervision of unconscious and sometimes gravely ill patients with the distribution of lunches or the issue of bed pans! Recovery beds may be placed near the operating theatre where they can be visited at frequent intervals by the anæsthetist in charge, who is immediately available in case of necessity. Harold Griffith [2] lists the advantages as follows :

Patients receive expert and immediate care during the critical period of recovery from anæsthesia and operation.

All emergency equipment is available and kept in good condition. Floor nurses are saved time and worry, since the patients are not returned to the wards until they are conscious and in fairly good condition. Student nurses are given supervised instruction in the immediate post-operative care of patients. The recovery room may be used as an emergency ward for the treatment of shock or unconsciousness from any cause.

The average stay of patients in Griffith's recovery room is less than one hour. Most hospitals could more easily provide a recovery ward situated in some other part of the building than the theatre block, where patients might remain for the first twenty-four hours. Such segregation would be a boon to the inhabitants of the surgical wards who were in the pre-operative or the convalescent phase of their treatment.

Treatment of Post-operative Complications

As the anæsthetist is responsible for pre-operative assessment of the patient and for his care during the operation, it is not unreasonable that he should take an interest in the treatment of such post-operative complications as are not, by their nature, the direct responsibility of the surgeon—notably the post-operative pulmonary complications. Many of us have had the opportunity of treating such complications, but only sporadically. That we do not do so more regularly is, I think, largely our own fault. If we were more assiduous in our post-operative follow-up of our patients, we would more often be the first to diagnose such complications; from this it is an easy step to secure the surgeon's agreement to our taking part in the treatment.

I have touched on some directions in which we can extend our activities with benefit, I think, to all concerned. The management of the pre-operative out-patient clinic, the charge of the resuscitation ward, of blood transfusion, intravenous therapy and oxygen therapy, a share in the care of the patient after operation, the performance of therapeutic and diagnostic nerve blocks, of bronchograms and of arteriograms, with the occasional

administration of an anæsthetic, should provide fare to satisfy the appetite of the most avid anæsthesiologist!

Developments of Anæsthetic Technique

One of the most impressive changes, to my mind, of the past ten years, has been the appearance of large numbers of anæsthetists whose knowledge and technical skill approach that of the best of the pre-war years.

A dramatic change came with the provision, through the E.M.S., of a reasonably efficient anæsthetic machine in every hospital in the country. We have enough trained anæsthetists who are capable of displaying the undoubted advantages that can be derived from these machines; but it is still not sufficiently widely appreciated by hospital authorities that they are potentially dangerous, and we hear, from time to time, of tragedies arising from their improper use by the ill-instructed. They would be safer if fitted with non-interchangeable couplings, but, as these couplings extend only from the regulators to the flowmeters, they may be a snare and a delusion while it remains possible to connect the wrong cylinders to the regulators. Two deaths occurred during the use of a machine of recent design which is foolproof except in this one respect and which may, therefore, have lulled the anæsthetists into a false sense of security.

We have seen the widespread adoption of the carbon dioxide absorption technique and of the use of cyclopropane, which was little more than a name to the majority of anæsthetists ten years ago. Our first enthusiasm for cyclopropane has waned and we now appreciate that there are occasions when ether is preferable.

Our attitude towards apnœa during anæsthesia has changed in a remarkable way. It is to-day only a minor incident in those cases in which it is not produced deliberately in the establishment of controlled respiration. This latter is now a valuable part of our armamentarium though I feel that many who employ it do not fully understand the dangers of under-ventilation with an accumulation of carbon dioxide: the terms cyclopropane shock and curare shock have been added to our vocabulary.

Waters has undertaken an assessment *de novo* of chloroform and we await with interest his final verdict. I have held for some time that if chloroform were a new discovery, used sparingly as an adjuvant to nitrous oxide and oxygen, we should hail it as a great improvement on all existing anæsthetic agents.

We have been introduced to trichlorethylene. The pendulum of favour has swung more than once and has not yet come to rest. There have been deaths associated with its use in anæsthesia but usually, I think, where there has been an incomplete appreciation of its limitations. I value it chiefly for its truly impressive analgesic properties; used intelligently for the production of analgesia it is probably completely safe, and I feel that it is for this purpose, in the main, that we shall retain it in our armamentarium.

Encouraging tales of new ethers are coming from the United States but we have, so far, little experience of them in this Country. Though we understand their limitations and disadvantages, most of us still rely, largely, on nitrous oxide and ethyl ether, which have survived more than a century of clinical trial. Our efforts to overcome their limitations and to reduce their disadvantages have produced the most dramatic development of recent years—the introduction into anæsthetic practice of extracts of curare. Though *d*-tubocurarine chloride has been widely used for some years and has been freely discussed at meetings of this Section we cannot yet claim to have mastered it [4, 5, 6]. Some of us have seen bronchospasm and massive collapse of the lungs, others have been more fortunate. These complications have been attributed to the release of histamine, but I understand that, with the doses of tubocurarine usually employed, the amount of histamine released is too small to have an effect except on the hypersensitive patient. It could be that these patients have been hypersensitive to histamine, and it is a subject that would repay investigation; but I think the ill-effects are more probably associated with variations in anæsthetic technique. The position is complicated by the fact that we are now enabled to provide satisfactory operating conditions at a much lighter level of general anæsthesia than was previously possible. At such a level of anæsthesia we should expect to see reactions we have not seen before and I feel that this, rather than any inherent fault of tubocurarine, is responsible. So far as I have been able to follow these cases, it appears that they are associated with the presence of a tracheal tube—a potential source of reflex disturbances—in light anæsthesia from thiopentone and cyclopropane, both drugs that tend to enhance the activity of the parasympathetic nervous system. In our present state of knowledge of tubocurarine I feel we would be wise to avoid tracheal intubation where we can safely do so: to maintain true surgical anæsthesia, preferably, in the lower first plane: and to use ether, which we know to be a bronchodilator, as our main anæsthetic agent.

There are now a number of substitutes for *d*-tubocurarine some of which, we feel, may have been placed on the market without sufficiently full investigation. Myanesin has been

fully discussed in this Section [3] and most of us feel that, in its present form, it is not suitable for use in anæsthesia. Flaxedil is effective and its use has, so far, disclosed no important disadvantages. Decamethonium is effective and is, perhaps, better than the others for oral endoscopies and for such operations as appendicectomy because of its shorter action. Unfortunately, with compounds having a relatively small molecular weight, the potency of a given weight of the salt varies inversely with the weight of the attached halide radical. Here we use decamethonium iodide; in the United States one firm markets the much more active bromide; another marks on the label the weight of the decamethonium radical! We are promised more synthetic muscle relaxants, and new alkaloids of curare are on the way. I would like to see all such drugs labelled in terms of their relative potency to the standard, *d*-tubocurarine chloride. The prospects of confusion are, otherwise, appalling.

Though basal narcosis, in the sense of pre-anæsthetic unconsciousness, is almost universally practised, we have seen the virtual abandonment of avertin and the widespread adoption of thiopentone.

We have some new tubes, but there have been no changes in the principles or practice of tracheal intubation except the introduction of Macintosh's curved laryngoscope blade. Though views as to the general applicability of this will vary, there can be no doubt of its value in certain cases. Tracheal intubation is now more widely and, in my opinion, too light-heartedly practised. There are many clear-cut indications for intubation; but it does represent a potential source of additional trauma to the patient and should not be used without good reason. There is a movement, with which Magill has associated himself, towards preference for orotracheal to nasotracheal intubation on the grounds that it permits the employment of a larger tube. While a tube the size of the trachea may be essential to an athlete running a race, a very much smaller one is large enough for a patient breathing quietly under anæsthesia: and I feel that Magill's blind nasal intubation is less often injurious than the laryngoscopy that usually accompanies orotracheal intubation.

New problems, which have been introduced by thoracic surgeons, have been overcome by use of the already established techniques of bronchial intubation and bronchial blocking with or without suction. These manipulations are difficult, not always successful and often traumatic. There is an increasing tendency to use tracheal intubation alone, with postural drainage of "wet" cases in the prone rather than in Beecher's original lateral position.

The last ten years have seen the introduction of the continuous spinal and continuous epidural techniques, but these are not yet widely used in this country.

There has been, however, a widespread revival of interest in local and regional blocks though we are still a long way behind the standard of knowledge and practice to be found in the U.S.A. and Canada. This was brought home to me by a particularly effective demonstration in the nerve block clinic of a French hospital in Montreal. The only new technique that has appeared here recently is the vagus nerve block of Macintosh and Mushin.

A novel practice is the attempt to control hæmorrhage by a deliberate lowering of blood pressure with Gillies' total spinal block (7) or by partial exsanguination through an arterial cannula, controlled with auto-transfusion. Scurr has recently achieved this effect by injection of pentamethonium iodide, a substance with a similar action to tetra-ethyl-ammonium iodide. Though there are a few operations where bleeding *must* be minimized, the widespread adoption of this principle will, surely, lead to frequent reactionary hæmorrhage.

Anæsthetic Records

The recognition of our imperfections has produced a greater interest in the search for better methods of anæsthesia. Few of us have opportunities for pharmacological or physiological research, none comparable with those available at some centres in America. The use of anæsthetic records, usually on Nosworthy's card, is now general. Such records are of great value in focusing the attention of the anæsthetist on any oddities in his patient's behaviour and will help to draw attention to such oddities as recur from time to time. It is unwise, however, to attempt to draw more than limited conclusions from these: it is not possible to record in detail everything that happens to every patient before, during and after operation. A line of investigation, suggested by inspection of routine records, must be carefully planned if it is to lead to reliable results with a reasonable economy of time and material. We have become aware of the value of statistics and we now realize that much painstaking work, on the conclusions drawn from which some of our practice is based, is completely valueless and must be repeated. Yet a statistical analysis is no better than the data on which it is based: with so many potential variables, careful and critical observation is the first essential.

The question of deaths under anæsthesia has always been a matter of concern to us and we are disturbed at the large number that we feel are avoidable. Chloroform fell into disrepute because of its dangers; from such figures as we have, it seems that thiopentone is much more lethal though the fault lies, probably, in the method of use. No one anæsthetist is likely to have a sufficient experience to be able to draw conclusions for the guidance of his fellows. We hope much from the investigation recently started by the Association of Anæsthetists.

The future affords unlimited opportunities for interesting, stimulating and extremely satisfying work. We are aware of the deficiencies of our handling of the agents available to us. The ideal anæsthetic agent has yet to be discovered—it may be that the pananæsthetic will prove as elusive as the panacea. For the present we can do best by using a judicious combination of anæsthetics and adjuvants. In 1938 I was accused of practising polypharmacy—nowadays we call it balanced anæsthesia. But I would urge the younger anæsthetists to realize that it is impossible to handle satisfactorily these complicated mixtures until one has mastered the use of the separate ingredients. In recent years we have made anæsthesia infinitely more pleasant for the patient and we have made notable advances towards the provision of ideal operating conditions for the surgeon. We have not made anæsthesia safer, and until we have done so we cannot be satisfied.

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Section of Physical Medicine

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Effects of Faulty Posture

PRESIDENT'S ADDRESS

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LITTLE attention has been directed in recent years to the relation between disturbances of posture and disorders of the locomotor system. This is largely to be accounted for by the recognition of the prolapsed intervertebral disc and its clinical implications. Another contributory factor is that the standard of postural treatment is often inadequate, in consequence of which results of treatment are poor. It can readily be appreciated that belief in the importance of postural treatment is likely to diminish if patients, for whom such treatment is prescribed, repeatedly fail to make symptomatic or structural improvement.

In what may be called the orthopædic era of low back and sciatic pain, when lumbosacral and sacro-iliac strains were considered the most important causes of these disorders, attention was naturally directed to the mechanics of the back. Between 1929 and 1939 numerous papers on posture appeared in the medical literature; the White House Committee on "Body Mechanics" reported in 1934, and the first two editions of the celebrated book by Goldthwait, Brown, Swaim and Kuhns appeared in 1934 and 1937. Now that the prolapsed intervertebral disc is held—almost certainly correctly—to be the most important cause of sciatic pain, and is also considered by some—almost certainly incorrectly—to be the most important cause of low back pain, interest in the mechanics of the back has diminished and contributions in the English and American literature are few and far between.

In this lecture three arguments will be developed; first, that notwithstanding the prolapsed intervertebral disc, there is a significant relationship between faulty posture and low back pain; second, that pain in the limbs and in other parts of the back are often to be attributed to postural defects and, third, that corrective postural treatment carefully worked out and purposefully carried out, greatly benefits a large group of patients attending Departments of Orthopædics and Physical Medicine.

NORMAL POSTURE

Posture can be regarded from the different viewpoints of the physical educationalist, who is chiefly interested in form; the anatomist, who is chiefly interested in structure, and the clinician whose main interest lies in the relation of posture to disease. Opinion of what constitutes good posture has undergone many changes in the course of time, and in the past has often been influenced by æsthetic and utilitarian considerations. The Greek idea of good

posture can be judged by studying their statues; it embodies the characteristics of the supreme athlete who in those times was an all-rounder. It might be thought nowadays when athletics are increasingly popular that we should return to the Greek ideal of posture. We find, however, that there are no special postural features characteristic of the athlete. Rather is there marked lack of uniformity, some athletes in the highest class showing postural defects of the back and even of the feet.

In the past, physical educationalists exerted an important influence. We find, for example, that it was they who encouraged the lumbar lordosis and prominent chest which was particularly common in Germany, and also in the Sergeant Majors of most countries. This posture was encouraged as it gave the impression of domination and strength. Not many years ago a reaction set in against the lordotic stance and people were encouraged to develop the flat back, which, as Wiles (1937) and others have shown, is not infrequently associated with low back pain. The extent to which physical educationalists have been prepared to go is shown in the following statement from a book of gymnastics quoted by Appleton (1946). "In women the shoulders should not be drawn back as this would appear unbecoming and defiant." The æsthetic and utilitarian aspects will evidently not carry us very far.

From the point of view of anatomy, no rigid rules can be laid down owing to the large variation in the physique of members of a community. Those who are familiar with Sheldon's classification (1940), and study his illustrations (Fig. 1, A, B, C) of extreme ectomorphy, mesomorphy and endomorphy will appreciate the need for a wide definition.

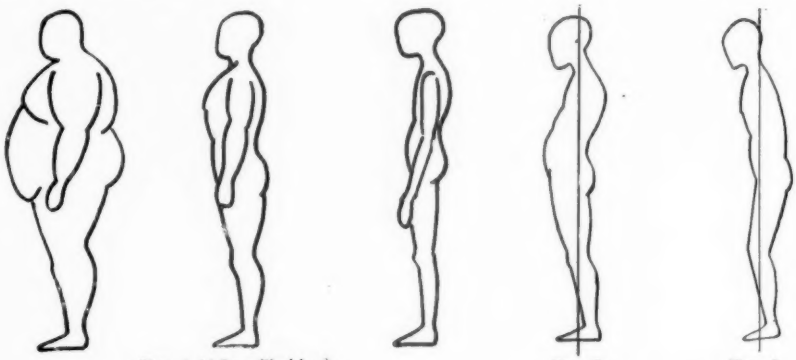


FIG. 1 (After Sheldon).

(A) Extreme ectomorphy.

(B) Extreme mesomorphy.

(C) Extreme endomorphy.

FIG. 2. Forward carriage of pelvis. Compensatory backward sway. Gluteal cleft in front of heel.

FIG. 3. Backward carriage of pelvis. Compensatory forward sway. Gluteal cleft behind heel. Flexion of knees.

Certain rough tests are of considerable help to the clinician. The first of these is to suspend a plumb line from the tip of the mastoid process. The plumb line should pass through the greater tuberosity of the humerus, the great trochanter of the femur, and through a point about $1\frac{1}{2}$ inches in front of the lateral malleolus. The last point is at the level of the tuberosity of the tarsal scaphoid. The plumb line will not pass through all these points if, the chin is poked forward, the shoulders are rounded, or if there is forward or backward carriage of pelvis.

The next rough test is to observe the pelvic carriage, the significance of which has repeatedly been emphasized by Appleton (1944, 1946, 1949). Normally the upper end of the cleft of the buttocks is approximately in the same vertical level as the back of the heel. With a forward pelvic carriage (Fig. 2) the ankle is dorsiflexed and the pelvis is over the front instead of the back of the foot. To restore balance of the body which is thereby disturbed adjustments in the back have to be made, the commonest of which is a backward sway in the dorsilumbar spine. Less frequently except in pregnant women (Appleton, 1944) there is backward carriage of the pelvis, the essential feature of which is flexion at the knee. To compensate disturbance of balance the trunk comes forward (Fig. 3) and a posture described by Wiles (1937) as "Round Back Type I" is produced.

The pelvic carriage is measured by observing the position of the intergluteal cleft relative to the back of the heel, the permissive range lying between 2 inches in front and ½ inch behind (Appleton).

Neither of the two tests described above provides any indication of the curves of the spine. The lumbar region is most conveniently studied by the measurement of the pelvic angle for which purpose Wiles devised a special inclinometer. The two points advised by Wiles are the upper part of the symphysis pubis in front and the posterior superior iliac spine behind. Appleton prefers the anterior superior iliac spine to the symphysis but also uses the posterior superior spine. The normal angle with Wiles's points is about 30 degrees, with Appleton's 5–10 degrees, an increased angle denoting a lumbar lordosis, a decrease denoting a flat back.

The cervical and dorsal curves are judged by noting respectively the relation of the back of the head and the most prominent part of the dorsal spine to the gluteal cleft. A cervical kyphosis is present if the occiput is more than 2 inches in front of the cleft, a lordosis if the back of the head is over half an inch behind. The dorsal curve may be considered abnormal if its more prominent part is over half an inch behind the gluteal cleft.

Types of Faulty Posture

(1) *Lumbar lordosis.*—Though lumbar lordosis is an important variety of faulty posture, the impression often given that it is the most important and most common postural fault is untrue. The features are as follows, there is an increase of the pelvic angle, overaction and later shortening of the erector spinæ and hip flexors, and weakness and stretching of the glutei. Often the abdominal muscles are also stretched and weak, but this, contrary to the general opinion, is not invariable. Moreover, as Wiles has pointed out, contraction of the abdominal muscles unaccompanied by contraction of the glutei has no effect in tilting the pelvis, and therefore no effect in correcting lordosis. That is not to say that poor abdominal musculature may be ignored, for clearly with a protuberant abdomen and consequent displacement of the abdominal organs the centre of gravity of the body is altered and needs correction.



Fig. 4.
Shop-girl's hip. L. buttock protruding. Weak and stretched L. gluteus medius. R. knee bent.



Sway back. Type I. (Wiles's round back Type II).



Sway back. Type II. (Wiles's sway back)

Common features: Tight pectoral muscles; weak rhomboids; forward carriage of pelvis; weak abdominal muscles.

Differences: Decreased or normal pelvic tilt (Type I); Increased pelvic tilt (Type II).

Fig. 5.

(2) *Shop-girl's hip.*—The term "shop-girl's hip" was used by Wesson (1938) to describe a relatively common postural fault in which the subject habitually stands with one knee bent, and the opposite buttock pushed out. This results in stretching and weakness of the gluteus medius and sometimes the Trendelenburg test is positive. Clinically patients with "shop-girl's hip" may present in one of three ways, with postural backache, with "swelling of the hip", with pain referred to the abdomen which, if on the right side, is often diagnosed as appendicitis. There have been innumerable instances of removal of a normal appendix when what was required was a course of postural exercises, and at least one patient had an unnecessary exploration for a tumour of the buttock.

(3) *Flat back*.—The term "flat back" is self-explanatory. The condition as a rule occurs in young women and gives rise to backache which is often resistant to treatment.

(4) *Sway back*.—The most common type of faulty posture encountered at the present time is the "sway back". There are two variations of the fault, and this often gives rise to confusion in terminology. It should be realized that the essential feature of both varieties is the same, namely a forward carriage of the pelvis. The difference between the two lies in the pelvic inclination. In Type I, which in my experience is the more common, there is no increase in the pelvic angle (there may even be a slight decrease), and the sway starts in the mid or upper lumbar region. In the less common Type II there is an increase of pelvic inclination and the sway begins at the lumbo-sacral junction. In both types of sway back other features are usually present, namely weakness of the abdominal muscles, tightness of the pectorals and poking forward of the chin.

In his classification of posture Wiles restricts the term sway back to the second type; for the first he uses the term "Round Back Type II".

(5) *Dorsal kyphosis*.—According to Wiles dorsal kyphosis usually follows dorsal epiphysitis (Scheuermann's disease), and Windle (1945) also found that a large proportion of young soldiers with dorsal kyphosis attending the Army Physical Development Centres showed evidence of epiphysitis. Dorsal kyphosis is also a common finding in middle-aged chronic bronchitics. The postural fault is invariably accompanied by rounding of the shoulders, tight pectorals and poor rhomboids.

(6) *Poking chin*.—The last type of deformity to be discussed is "Poking Chin" (Fig. 6). The features are as follows: there is an obliteration of the cervical lordosis and a compensatory tilting back of the head at the atlanto-occipital joint. In the posterior cervical muscles there is stretching and weakness of semispinalis cervicis and overaction with ultimate shortening of semispinalis capitis. The corresponding flexor muscles in front, namely, longus cervicis and longus capitis shorten and lengthen respectively. In middle-aged women in whom this postural fault is relatively common, a pad of fat over the seventh cervical and first dorsal spines may develop, to which the name of "the dowager's hump" is sometimes given.



Head tilted back at atlanto-occipital joint.
Chin forward.
Decreased cervical lordosis.
Stretching and weakness of semispinalis cervicis and longus capitis.
Shortening of semispinalis capitis and longus cervicis.

FIG. 6.—Poking chin.

FINDINGS ASSOCIATED WITH FAULTY POSTURE

There are certain findings associated with faulty posture which occur so frequently, and which often appear to play such an important part in the production of symptoms that it seems reasonable to ask if it is the postural fault with which we should primarily be concerned, or a collection of findings of which the anatomical defect is one. Are we, in fact, really dealing with a syndrome of faulty posture? Associated findings are three in number and consist of inability to relax muscles, diminished agility, and limitation of movement of the spine.

Incomplete muscular relaxation, often over a wide area, is present in the majority of patients with long-standing pain in the back. It is often described as muscular spasm and is regarded as a protective mechanism. That protective muscle spasm does occur cannot be denied, but it is usually in response to acute pain. The "spasm" under consideration occurs when pain is not acute; it may affect single or multiple groups of muscles. An example of incomplete relaxation in a single muscle group is seen in patients with chronic lumbar pain. When such patients lie comfortably on a couch in the prone position, even under a heat lamp, the erector spinæ remain tense even though no pain is experienced at the time. Prolonged treatment may be necessary before such patients are able to relax their muscles, but when the habit of relaxation has been re-acquired symptoms almost immediately start to improve. Until then, however, progress is slow. An example where many groups of muscles are involved is seen in long-standing acroparæsthesia, where the head, neck and shoulders are held tensely and the muscles of the arm and forearm are tight. The latter may be the predisposing cause of pain in the elbow which not infrequently complicates acroparæsthesia.

Inability to relax muscles produces or increases fatigue muscle pain; it also ultimately leads to muscular wasting, for a muscle which never fully relaxes never fully contracts, and a prolonged period of incomplete muscular contraction is followed by wasting.

Lack of agility and movement may be considered together. There are two chief causes, first, incomplete muscular relaxation described above, and second, the result of adhesions either between the muscle fibres or between muscle groups. These adhesions which were described by Gratz (1937) interfere with normal contraction of muscle and also with the gliding of one muscle over another.

When abnormal posture has been maintained for a long time shortening occurs in muscles, ligaments and joint capsules, and in severe cases there may be alteration in the shape of the vertebræ. In these instances full correction by non-surgical methods is out of the question.

Clinical Sequels of Faulty Posture

The clinical conditions associated with faulty posture may conveniently be considered under three headings. Fatigue muscular pains in any part of the back constitute a primary group, acroparæsthesia, back strain and chronic recurrent cervical fibrositis constitute a secondary group, and osteo-arthritis of the hip and lumbar spine a late secondary group.

Primary Effects

In a Department of Physical Medicine patients are frequently seen with a history of pain in one or other region of the back which develops during the day, is made worse by long periods of standing and is relieved by rest. The pain is of a dull aching character; it is never acute or stabbing, and after a night's rest the back feels entirely normal. As time goes on the aching pain develops earlier in the day, but for months, and often for years, the response to rest is unchanged.

Muscle fatigue is the probable explanation for these symptoms. Its cause is that either the muscles are too weak for prolonged use, or that they are playing too great a part in the maintenance of the upright posture. The backache associated with a flat back is an example of pain arising from a muscle which is too weak. The pain occurring with a lumbar lordosis is an example of a muscle having too much to do, for with lumbar lordosis the upright posture instead of being maintained by equal action of the erector spinæ and glutei is maintained by the erector spinæ alone.

Secondary Effects

A. Acroparæsthesia.—A great increase in the incidence of acroparaesthesia has been noted by many. The symptoms consist of pain down the arm, numbness and tingling in the hands of both sides, nearly always worse at night and first thing in the morning. Throughout the night the victim is awakened by "pins and needles" in the fingers and in the morning the arms ache and the fingers are clumsy, so that it is difficult to pick up a cup of tea and not infrequently the cup is dropped. Such activities as carrying baskets and ironing clothes invariably aggravate the condition which affects members of the female sex almost exclusively, the victim as a rule being a middle-aged woman. On clinical examination abnormal physical signs are absent with the exception of horizontal clavicles and some drooping of the shoulders.

For many years the condition was diagnosed as brachial neuritis. The opinion has recently been put forward by Walshe, Harvey Jackson and Wyburn Mason (1944), that acroparæsthesia is due to an altered relation of the shoulder girdle and thoracic outlet secondary to poor tone of the shoulder girdle muscles. Traction and compression of the lower cord of the brachial plexus and possibly also the subclavian artery are the essential mechanical factors underlying most, if not all, cases of acroparæsthesia in women.

Walshe's (1945) clinical description of acroparæsthesia cannot be improved upon. His remarks on treatment, however, require some qualification: "Treatment" he writes, "is generally allowed to be unsatisfactory and includes radiant heat, massage, ionization and diathermy and when the desperate patient has sought relief from practitioners not on the Medical Register, manipulation of the spine is still further added to her torments." If acroparæsthesia is in fact caused by sagging of the shoulder girdles, radiant heat, massage, ionization, diathermy and manipulation cannot be expected to have any effect. The only logical method of treatment is to correct the sagging of the shoulders by improving the tone and strength of the shoulder elevator muscles. This is borne out by results when treatment along these lines is carried out.

B. Back strain.—A common cause of acute back pain is a tear of a muscle, joint capsule or ligament. Such a tear or "strain" is likely to occur at the junction between elastic and less elastic tissues, or between elastic and non-elastic tissues (Cohen, 1948), a common site being the attachment of muscle or ligament to bone. For example, it occurs in the back where the muscles are attached to the transverse processes of the vertebræ, and also where the inter-spinous ligaments are attached to the spines. The reason why strains are particularly common in subjects of faulty posture is because of their lack of agility and limitation of movement. The normal, mobile back can adapt itself to sudden and unexpected movements. The back moves quickly and there is a large range over which the spine can move without over-stretching muscles or ligaments. The spine which is not agile cannot react quickly to the unexpected, and a clumsy, abnormal movement is made. Moreover, if there is also shortening of muscles and ligaments, a sudden or relatively large movement is likely to cause a tear. There was a great increase in the incidence of back strain in the earlier part of the war when middle-aged and elderly gentlemen, who were quite unused to exercise, took to gardening. In the majority of instances the spine was found to move slowly, movement was often limited and posture abnormal.

C. Chronic recurrent cervical fibrositis.—Though not, strictly speaking, a direct consequence of faulty posture, chronic recurrent cervical fibrositis may be considered here owing to the frequency with which it is found in association with "poking chin". Many patients give a history of having received repeated courses of heat, massage and other forms of physio-therapy. Often relief has been obtained, but, as a rule, it has been partial and temporary. A great difference can often be made to these unfortunate people if, in addition to physio-therapy given to relieve pain, the postural defect is also attended to.

It is not suggested here that all cervical fibrositis is due to bad posture. It is, however, pointed out that fibrositis and bad posture are commonly associated, that faulty posture is undoubtedly an aggravating feature and that it may also be an important predisposing cause.

Late Secondary Effects

A. Osteo-arthritis of the hip.—Osteo-arthritis is likely to occur in joints whose mechanics have been seriously disturbed, whether by disease, deformity or trauma. The association of faulty body mechanics and osteo-arthritis of the hip has been emphasized by Kuhns on more than one occasion (1934, 1942). Normally at the hip-joint the weight of the body is borne by the central portion of the femoral head in contact with the strong upper portion of the acetabulum. Whenever this is not the position of use, as is the case when an increased forward inclination of the pelvis accompanies faulty body mechanics, disalignment results and osteo-arthritis is likely to occur.

Kuhns (1942) treated a series of 183 patients with osteo-arthritis of the hip by conservative rather than surgical treatment. The aim of treatment was to restore normal weight bearing as much as possible, and this was achieved with exercises concentrated on correcting the lumbar lordosis and improving the tone of the glutei. Where necessary patients were fitted with a low back support. The end-results of treatment were striking. Of the 158 patients who were followed up 47, including 28 with bilateral osteo-arthritis, returned to work free from symptoms, and another 58 had slight symptoms only. Important points raised by Kuhns are, therefore, first, that there appears to be a significant relation between faulty posture and osteo-arthritis of the hip, and second, that attention to body mechanics is likely to have beneficial results on osteo-arthritic patients.

With regard to ankylosing spondylitis Swaim (1949) states first, that in spondylitic patients whose posture is good, hip involvement is rare; second, that if attention is paid to posture in the early stages of the disease, hip involvement can usually be avoided; finally, he quotes instances of spondylitics with hip involvement where great improvement of hip function resulted from correction of faulty posture.

Treatment

There is perhaps no form of physiotherapy which requires more accurate performance than the correction of faulty posture. Minor errors of judgment are likely to have serious effects on the result of treatment and may nullify it altogether.

In the treatment of faulty posture five factors have to be considered: improvement of agility, improvement of mobility, re-acquisition of the ability to relax muscles, improvement in the strength of weak or relatively weak muscles and finally re-education of the postural reflex, that is to say, the patient must be taught automatically to adopt the correct posture

and to maintain it in all circumstances. In planning treatment it is necessary to assess these five factors for each individual and list them in order of priority, for it must be realized that their relative importance varies from patient to patient. For example the most important factor with a flat back is that the muscles are weak, and in such a case the emphasis must be laid on improving their strength. In the sway back re-education of the postural reflex is the most important factor. With a dorsal kyphosis it is usually lack of mobility which must be dealt with before symptomatic improvement will be obtained, while in many instances of lumbar pain associated with a lordosis an essential condition of improvement is the ability to relax the erector spinæ muscles.

Improvement of agility is best achieved with exercises in a class. The methods of obtaining improvement of mobility vary according to whether limitation is due to intermuscular adhesions, tightness of ligaments or shortening of muscles. Mobilizing exercises, in some instances supplemented with massage or faradism, may be expected to improve the first group. When there is tightness of ligaments, traction, continuous in severe cases, repeated in the less severe, is the method of choice, a halter being of value with lesions in the cervical and upper and mid-dorsal regions (Wiles). When there is muscular shortening care has to be exercised for it is generally agreed that forcible stretching of muscles is undesirable and may be dangerous. Wiles and others recommend that exercises against resistance for the antagonists produce complete relaxation of the shortened agonist muscles and ultimately lead to increase in their length.

Individual treatment is necessary in the early stages to teach muscular relaxation and also to re-establish a normal postural reflex. To start with individual treatment is also necessary for the teaching of specific muscle strengthening exercises. When these have been mastered the patient should join the class.

Failure of the exercises to achieve their object is almost invariably due to incorrect performance, and it is surprising what difficulty certain exercises present to certain patients. As a rule it is obvious when an exercise is being performed incorrectly. On other occasions it may be difficult to appreciate error unless one is alive to certain trick movements which are readily picked up and which often mimic closely the correct method. One exercise commonly ill-performed consists of a slow drawing backward of the neck starting with the chin on the sternum and ending with the neck vertical. The spine is moved segment by segment with the head kept flexed throughout at the atlanto-occipital joint. The object is to strengthen the semispinalis cervicis, to relax the semispinalis capitis and thereby improve the condition of "poking chin" and the symptoms that arise from it. Its correct performance depends on maintenance of flexion at the atlanto-occipital joint; failure occurs when flexion takes place at a lower cervical level.

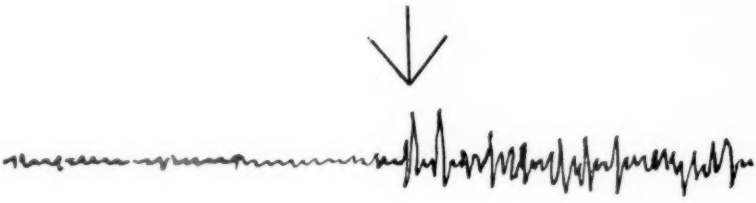


FIG. 7.—Electromyographic tracing with needle in semispinalis cervicis during performance of exercise for "poking chin".

An electromyographic tracing with the needle in the substance of semispinalis cervicis is shown (Fig. 7). In the first part of the tracing the exercise is incorrectly performed with flexion of the neck in the mid-cervical region. In the second part performance is correct, flexion being maintained at the atlanto-occipital joint. The tracing illustrates very well the great difference in motor unit activity when exercises are correctly and incorrectly performed. They also suggest that electromyography may provide a useful means of determining whether a newly devised exercise achieves what it sets out to do.

SUMMARY

(1) A wide definition of normal posture is necessary owing to the variations in physique in members of the community.

(2) Useful clinical information can be obtained from three tests: the plumb line, the pelvic carriage and the pelvic angle.

(3) The common varieties of faulty posture are: (1) Lumbar lordosis; (2) shop-girl's hip; (3) flat back; (4) sway back; (5) dorsal kyphosis; (6) poking chin.

(4) Features constantly found in association with faulty posture are: (1) Inability to relax muscles; (2) loss of agility; and (3) loss of mobility of the spine.

(5) The clinical sequels and accompaniments of faulty posture may be considered under three groups: primary (fatigue muscle pain), secondary (acroparæsthesia, back strain and chronic recurrent cervical fibrositis), and late secondary (osteo-arthritis of the hip and lumbar spine).

(6) Five factors have to be considered in treatment. Improvement of agility, improvement of mobility, re-education of muscular relaxation, strengthening of weak muscles, re-education of the postural reflex. These five factors vary from patient to patient.

(7) Unless treatment is carefully worked out and accurately carried out improvement is not obtained.

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Section of Medicine

President—Sir ADOLPHE ABRAHAMS, O.B.E., M.A., M.D., F.R.C.P.

[*October* 25, 1949]

DISCUSSION ON THE MANAGEMENT OF RHEUMATIC FEVER AND ITS EARLY COMPLICATIONS

Cardiac Complications

By PAUL WOOD, O.B.E., M.D., F.R.C.P.

IN any patient with active rheumatic fever or suspected rheumatic fever it is vitally important to detect the presence or absence of clinical carditis, for proper immediate and future management depends upon the accuracy of such a diagnosis.

Approximately 5% of the population are known to have acute or subacute rheumatism before they are 20 years old (Parkinson, 1945). Of those recognized at the time, about 5% die within one year, 10% within five years, and 20% within ten years (Coombs, 1924). It is estimated that there are some 200,000 adults between the ages of 18 and 41 with organic rheumatic heart disease in Great Britain at the present time; from the figures quoted above it follows that there would have been about 300,000 had there been no earlier deaths. Not more than 200,000 of these would be expected to give a rheumatic history, the incidence of such a history in all cases of mitral stenosis being about 66%. If the young adult population is put at 10,000,000, then there should be about 500,000 healthy persons who also give a history of rheumatic fever in childhood (Parkinson and Hartley, 1946). It follows that around 70% of cases escape without detectable cardiac damage, or recover from it completely. As the latter event is rare, the statement that carditis may be assumed for all practical purposes in active rheumatic fever cannot be accepted. If 10–20% recover completely from clinical carditis, then 50–60% escape entirely. This calculation agrees fairly closely with clinical observations during the acute stage of the disease. The incidence of carditis at Taplow is higher (72%), but this is almost certainly due to selection, cases recovering quickly having far less chance of being admitted.

The chief signs of active carditis may be listed as follows: (1) Significant mitral systolic murmur. (2) The Carey Coombs murmur. (3) A new or transient aortic diastolic murmur. (4) Cardiac enlargement. (5) Pericardial pain, friction or effusion; or electrocardiographic proof of pericarditis. (6) Elevation of the jugular venous pressure and other evidence of heart failure. (7) Prolongation of the P-R interval or of $Q\text{-}T_c$.

(1) *Mitral systolic murmur.*—A significant mitral systolic murmur is usually early in onset, long, loud and blowing. Follow-up studies reveal that 45% of children with loud murmurs, and only 9% of those with soft murmurs, develop permanent valve disease (Boone and Levine, 1938). Without the help of phonocardiography it is impossible to tell precisely when a murmur begins, and we have no information on this point concerning the early or relatively early mitral systolic murmur. But the late systolic murmur is easily recognized by auscultation and we have heard it in several patients with undoubted active carditis. Moreover, in cases of permanent organic mitral incompetence with a mitral systolic

murmur and thrill, left ventricular enlargement, and systolic expansile pulsation of the left auricle (Figs. 1 and 2) the murmur and thrill may be late (Fig. 3). Expansile pulsation of the left auricle is seen in a small minority of cases of active carditis with loud mitral systolic murmurs: follow-up studies on this group may prove interesting. Advanced organic mitral incompetence presents in two main forms: (1) with left ventricular enlargement (Fig. 3) when it is apt to be confused with aortic stenosis; (2) with aneurysmal dilatation of the left auricle (Fig. 4). Type I tends to develop irreversible heart failure in the fifties; Type II

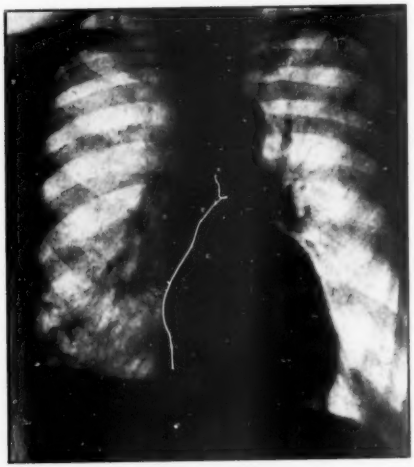


FIG. 1.—Case of permanent organic mitral incompetence showing dilatation of the left auricle.

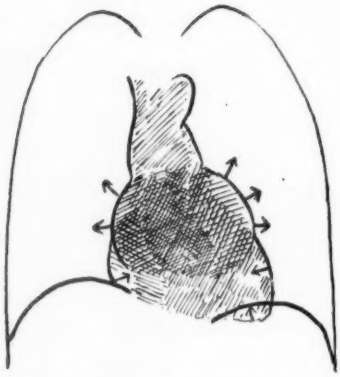


FIG. 2.—Diagram illustrating expansile pulsation of the left auricle during systole.



FIG. 3.—Case of permanent organic mitral incompetence with considerable left ventricular enlargement. In this instance the systolic murmur and thrill were late, and immediately preceded the second heart sound.

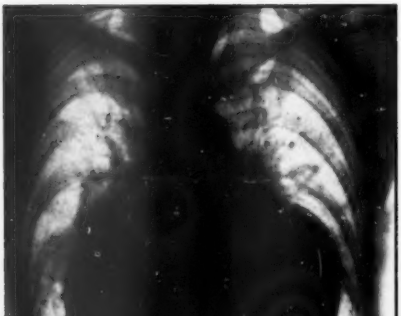


FIG. 4.—Case of organic mitral incompetence with aneurysmal dilatation of the left auricle.

behaves more like mitral stenosis. Early or mild cases are, of course, less characteristic and may show little but the murmur and paradoxical pulsation of the left auricle. Admittedly, organic mitral incompetence is uncommon, but it is hardly rare. I have collected some 20 good examples since 1937, omitting the war years.

(2) *Carey Coombs murmur.*—The notation is used to describe the soft, low-pitched, relatively short mitral diastolic murmur associated with active rheumatic carditis. Though it may be transient or recurrent, it usually persists or may be brought out by special circumstances when all other evidence of activity has subsided. It is heard best with the bell stethoscope during the inspiratory phase of quiet respiration when the patient lies on the left side. When mitral stenosis develops it becomes louder, rougher, and longer, and may be accentuated in presystole. We agree with Carey Coombs that this murmur is probably due to turbulence set up by thickening of the mitral leaflets. It cannot be due to left ventricular dilatation because it is common when the heart is not enlarged.

In a consecutive series of 105 new cases of rheumatic fever at Taplow, there were 75 with evidence of carditis. Of these, 58 developed a Carey Coombs murmur, permanent in 45 and transient in 13. Mitral valvulitis associated with an isolated systolic murmur occurred in only three cases, and these were admitted late in their course.

(3) *Aortic diastolic murmur.*—The first definite evidence of carditis may be a soft, high-pitched, short aortic diastolic murmur. It may be heard only with a Bowles type of stethoscope, being often inaudible with a bell type. A very short gap may be detected between its onset and the second heart sound, as described by Wells at a meeting of the Cardiac Society last year, but it precedes the third heart sound and does not give rise to the same cadence as the mitral triple rhythm. It is usually maximum in the third left space close to the sternal border, but may be louder lower down.

In our series of 75 fresh cases of rheumatic carditis at Taplow, 34 developed an aortic diastolic murmur, permanent in 30 and transient in 4. Combined mitral and aortic lesions occurred in 26 cases.

(4) *Cardiac enlargement.*—We have been disappointed in radiology as a means of detecting the presence of carditis. Enlargement of the heart shadow is unusual unless there is heart failure, pericardial effusion, or old valve lesions. Slight reduction of heart size may follow the subsidence of any fever (Weens and Heyman, 1946); on the other hand, other things being equal, the diastolic heart size is apt to be larger when the rate slows. With the short exposure times in common use nowadays, serial films may show hearts in systole or diastole, a simple trap for the unwary.

As previously stated, conspicuous enlargement of the heart without old valve lesions is nearly always due to failure, and occurs rapidly. The four examples shown died, and necropsy proved that there was no pericardial effusion. In patients who recover from failure enlargement is reversible. In the case illustrated pericardial effusion was excluded as far as possible.

(5) *Pericarditis.*—The occurrence of pericardial pain, friction or effusion provides good evidence of carditis, rheumatic pericarditis never occurring alone. We have experienced some difficulty in diagnosing fibrinous pericarditis without friction and in distinguishing pericardial effusion from a dilated heart in failure. The electrocardiogram has proved unexpectedly disappointing (Fig. 5), the pattern denoting widespread superficial myocardial injury being found in only 25% of proved cases. This is in sharp contrast to tuberculous pericarditis in which the pericardial T2 pattern is seen in practically all. It is suggested that the frequent absence of the current of injury may be due to the lack of a boundary zone between the superficial and deeper layers of the myocardium, owing to coincident carditis. If this hypothesis is correct, one would expect a better prognosis in those showing the current of injury. In fact, the majority of those that exhibited such a graph recovered, whereas the majority of those who did not, died; but the numbers are too few to be statistically significant.

Pericardial effusion may be proved by paracentesis, but a dry tap does not absolutely exclude it owing to the possibility of technical fault or difficulty. Three other methods of distinguishing it from a dilated heart are being investigated. (1) Skiagrams in the prone or supine position may show widening of the vascular pedicle, disappearance of the first inch of the descending aorta, and divergent vascular shadows near the thoracic outlet. So far we have been unable to distinguish pericardial effusion by this method. (2) The Q-T interval is lengthened in rheumatic carditis and tends to be shortened with pericardial effusion. Thus in 12 cases of rheumatic pericardial effusion $Q\text{-}T_c$ averaged 0·36 second, and ranged between 0·32 and 0·40 second. Very few, if any, cases of heart failure from active carditis have $Q\text{-}T_c$ intervals within this range. This is proving a useful method of distinguishing the two conditions provided digitalis has not been given (digitalis shortens the Q-T interval). (3) If the catheter is coiled in the right auricle, its tip can be made to lie against the right

auricular wall (Fig. 6). In pericardial effusion the right border formed by the parietal pericardium may lie well beyond the tip of the catheter (Fig. 7). Angiocardiography offers an alternative means of providing similar information, but is hardly justified in these sick children. Cardiac catheterization is far less unpleasant and is well tolerated.

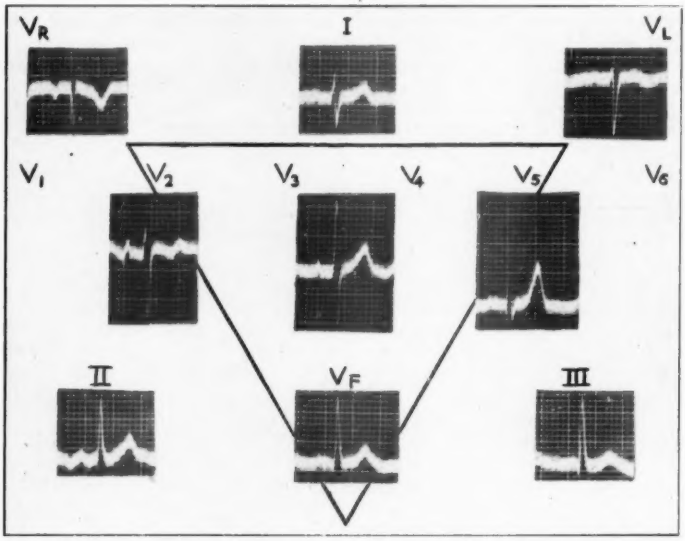


FIG. 5.—Normal electrocardiogram in a case of severe pericarditis proved at necropsy.

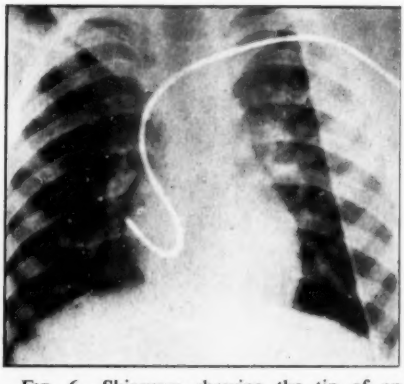


FIG. 6.—Skiagram showing the tip of an intracardiac catheter lying against the wall of the right auricle.

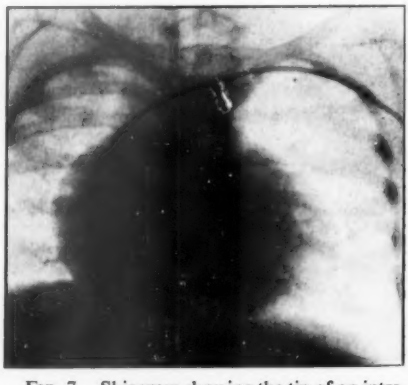


FIG. 7.—Skiagram showing the tip of an intracardiac catheter lying against the right auricular wall in a case of pericardial effusion.

(6) *Heart failure.*—The development of congestive failure is always grave, and the majority die within a few weeks or months. We have several observations to make about failure in active carditis.

(*a*) None of our patients died abruptly. In the literature the incidence of sudden death is also remarkably low—0·04% of cases or less than 1% of all deaths (Griffith and Huntington, 1946). Sitting up suddenly, being transported to the X-ray department for sitting films, cardiac catheterization, digitalis intoxication or reactions to other drugs have never caused ventricular fibrillation or cardiac standstill. In this respect there is a very great contrast

between the behaviour of rheumatic and diphtheritic carditis. Fortunately, the management of rheumatic cases need be influenced by no such ill-founded fears.

(*b*) The erythrocyte sedimentation rate falls in only about a third of the cases. We have not yet attempted to correlate this with changes in hepatic function, but on the whole the greatest drops have occurred in the more chronic instances.

(*c*) A low sodium diet has proved singularly disappointing; indeed heart failure from rheumatic carditis seems almost unique in its lack of response.

(*d*) On the other hand, digitalis may give excellent results. Slowing of the heart-rate, diuresis, loss of weight, increase of vital capacity, and cessation of vomiting accompany the fall in venous pressure and shrinkage of the liver. Cases that do not respond usually die. It is remarkable how well these children tolerate the drug and our early fears of the dangers of overdosage soon evaporated. The effective dose for an average child of about 10 is half rather than a quarter or third of the adult dose. Another interesting point about digitalis in active rheumatic carditis is that it may cause no depression of the ST segment of the electrocardiogram. One cannot help being reminded of the absence of ST deviation in so many of the cases of pericarditis, and wondering whether both peculiarities depend upon a common factor.

(7) *Electrocardiographic evidence.*—Prolongation of the P-R interval has occurred in barely 10% of our cases, but this may be because the majority are not seen early enough.

Prolongation of Q-T_c has proved a much more valuable index of activity. Details have been reported by Abrahams (1949).

Elevation of the ST segment and reversal of the T wave, due to pericarditis, have already been discussed.

The management of cases known to have carditis still follows traditional paths; they are usually kept in bed until all evidence of activity has subsided or until hope of its ever doing so is abandoned. There is no evidence that the natural course of the disease can be influenced in any other way, and precious little that it is greatly influenced by rest. However, it is up to those who believe that physical effort does no harm in the active phase of the disease to prove their point before we can be expected to give up so obvious a remedy.

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The General Management of Rheumatic Fever

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APART from the chemoprophylaxis of rheumatic fever and the use of cortisone and pituitary corticotrophic hormone, there is really very little on this subject that has not been said by many others in the last fifty years. There is, however, a fair amount of controversy over some of these traditional lines of treatment. I think this is largely because we have tended to rely on clinical impressions and inherited beliefs rather than on efforts to secure factual evidence. The great difficulty is, as always in clinical work, that we cannot run the risk of harming the patient by omitting measures we believe to be of value, even though the evidence for that usefulness is poor. We hope to secure data on the effects of treatment in the Special Unit at Taplow but it is much too early yet to give more than general impressions from this experience and although I shall cite particular instances and tentative impressions, we are not yet in a position to produce standard errors and coefficients of correlation.

The relative costs of caring for rheumatic children in their own homes, in foster homes, in convalescent homes and in hospitals are shown in Table I.

TABLE I.—RELATIVE COSTS OF CARE

Home care	:	30–35 dollars/month
Foster-home care	:	45–50 dollars/month
Convalescent home	:	120 dollars/month
Hospital	:	400 dollars/month

These are American figures but there is no reason to think that they differ very greatly (even after allowing for devaluation) from ours. Despite the great difference in cost I am convinced that it is better to care for these children in hospital. Rheumatism is a disease of the under-privileged and there is something in their home environment which is conducive to the disease and to its recurrence. In the occasional case occurring in a well-to-do home, home nursing may be the more desirable.

As existing methods of treatment involve a long stay, a hospital should have a school attached. It means a great deal to a child's psychological development to find when he rejoins his school, as most do after a period of six months or a year, that he has not lost his place and left his friends. It is better for one hospital to take care of the child from the start, as we are prepared to do at Taplow, and see him through: the present practice of admitting to a large general hospital and then after six or eight weeks discharging to a convalescent home is largely an economic makeshift, involving rupture of that personal contact between doctor, patient and family which is the most important factor in after-care.

Differential Diagnosis

The first thing in the management of acute rheumatism is to make sure that the case *is* one of acute rheumatism. The differential diagnosis in some cases is most important.

Table II.—Differential Diagnosis of Rheumatic Fever

In children:	*In adults*:
Appendicitis (19/271, Hansen)	*Subacute bacterial endocarditis*
Growing pains	*Gout*
Poliomyelitis	*Gonococcal arthralgia*
Osteomyelitis	Rheumatoid arthritis
Leukæmia	Lupus erythematosus
Still's disease	
Scurvy	
Congenital heart disease	
Rare blood diseases (Letterer-Siwe, myelosclerosis, sicklæmia)	

Thus in a case presenting as early osteomyelitis of the knee or hip it is far better to treat immediately with large doses of penicillin even if the case ultimately turns out to be rheumatic fever than run the risk of getting bone destruction and its crippling sequelæ. The distinction may be at times extremely difficult in the very early case. Appendicitis is perhaps the only other common difficulty. While it is no disgrace to open up an occasional rheumatic abdomen (because occasionally a true appendicitis occurs and needs such treatment), it seems probable that the majority of right lower quadrant scars in rheumatic fever patients could be avoided if this possibility were present more often in the mind of the surgeon (Hansen, 1943).

Still's disease with fever, joint-pain and swelling, and rash is also occasionally difficult to distinguish in its early stage: the action of salicylates on the fever is not, as used to be so widely taught, diagnostic of rheumatic fever.

Fourthly, clubbing and petechiæ are not always indices of subacute bacterial endocarditis when they occur in rheumatic patients. We have seen clubbing in rheumatic carditis with failure, in the absence of infection and lung disease, and it has receded completely as the child recovers. Such cases should not be allowed to vitiate the statistics of cured subacute bacterial endocarditis.

Rest in Bed

Management of rheumatic fever is based on the fact that it is a self-limited disease and the only sequelæ of any importance are the cardiac lesions. If these could be aborted the disease would be of no more importance than mumps. It has long been thought that the heart is less damaged if its work be cut down to the basal requirements of 40–50 cals/sq.m./hr. An extremely interesting analogy is poliomyelitis where Ritchie Russell (1949) has shown that severe paralyses occur in those who have indulged in considerable physical activity during the prodromal period. This cardiac rest is best achieved by keeping the patient lying flat in bed. Although it is known that the work of the heart is slightly more in the flat position than in a sitting position, the curtailment of activity is so much greater that the *total* cardiac work (as distinct from the *basal* cardiac work) is actually less, because less movement is possible. The evidence for this hypothesis that rest minimizes residual cardiac damage is scanty (Sibson, 1877) and it rests largely on clinical impressions. Perhaps the best evidence available is that of Taussig and Goldenberg (1941). They observed that of a group of children showing progressive enlargement of the heart and a 50% mortality, only half had been treated with bed rest and then only for a short time, whereas in other groups which showed no

progressive enlargement and a 6% mortality only, 98% had adequate periods of prolonged bed rest. As I have said before, few physicians, unless they hold strong beliefs to the contrary, would risk the ultimate wellbeing of their patients by omitting such prolonged rest. Yet in Chicago I have recently been shown a camp where children are encouraged to lead an active supervised life—boating, swimming, &c.—even though they may have an E.S.R. in the neighbourhood of 40 mm./hr.: the only criterion is that the E.S.R. should be beginning to show a definite fall. It is claimed that no harm results from this. Unfortunately the assessment of such measures involves a long survey and follow-up of a large number of rested and non-rested cases and that requirement has not yet been fulfilled.

Criteria of Rheumatic Activity

The critical question, accepting rest as the most important measure in the treatment of rheumatism, is "for how long?" and, on the above hypothesis, it should be not for any arbitrary period of six months but until carditis has completely subsided. What criteria should we use for this? Fig. 1 shows the criteria that we are actually using at Taplow. It

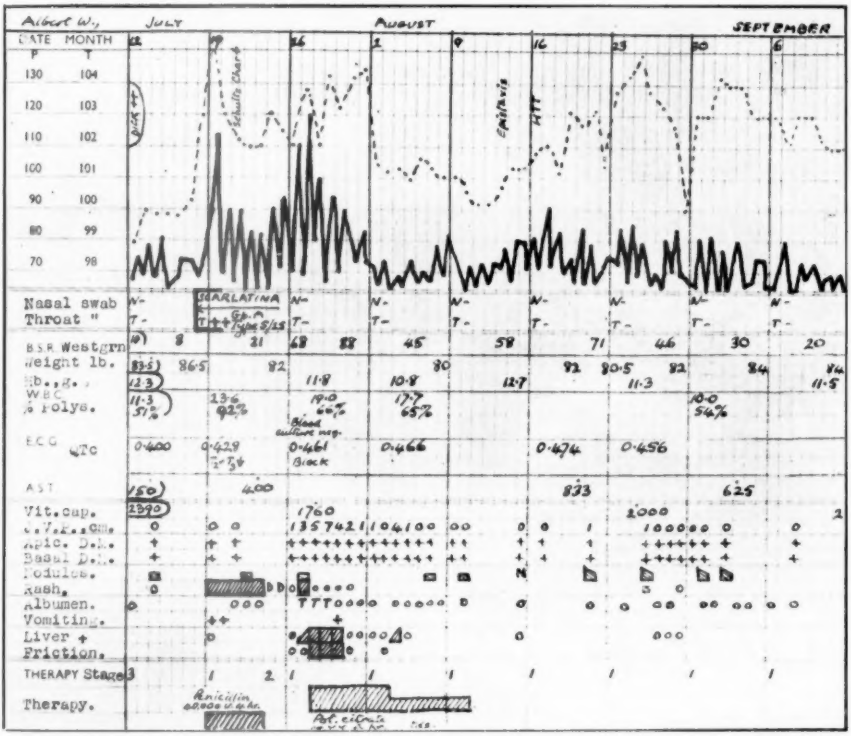


Fig. 1.—Routine ward chart (Canadian Red Cross Memorial Hospital, Taplow), showing rheumatic attack following scarlatina.

shows an attack of scarlet fever occurring in a convalescent rheumatism patient. Of the clinical observations, pulse and temperature are important but some children will show bradycardia during the active phase and some are afebrile. Hæmoglobin rise indicates recovery but it may be delayed. The white blood count is of only limited value. The anti-streptolysin O titre merely indicates a previous Group A hæmolytic streptococcus infection and is of no value in this respect at all. The sedimentation rate is one of the most useful of criteria and is perhaps more widely used than any other. We depend largely on the weekly sedimentation rate and prefer the Westergren technique. We feel that correction for anæmia is worse than useless: anæmia itself is an indication of activity and adds to the value of the

reading. There is also less packing than in the Wintrobe tube for the hour reading. It should be remembered, however, that there are certain fallacies in this test. Firstly, during failure, sedimentation rate may fall, as Payne and Schlesinger showed in 1932. Secondly, salicylates, admixture of alcohol in the syringe and a low ambient temperature depress the sedimentation rate. Thirdly, a high E.S.R. may occur in adolescent girls without rheumatic activity, shown in Fig. 2. The high level may be maintained for months or it may finally become normal.

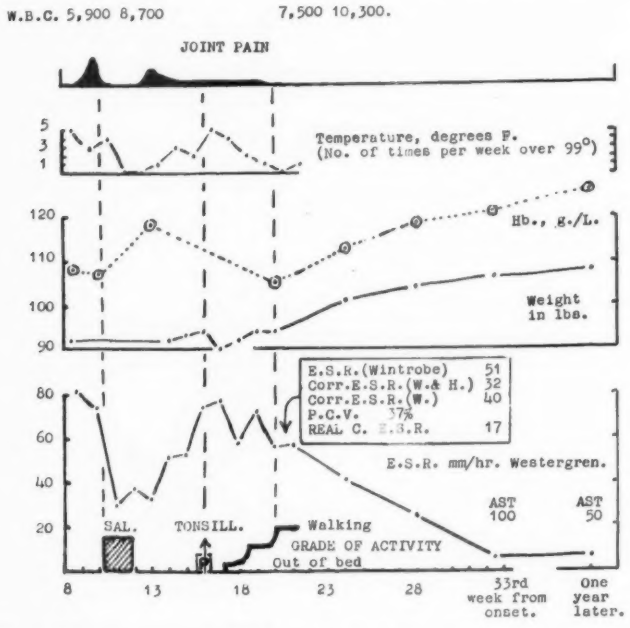


FIG. 2.—Chart showing decrease in E.S.R. with salicylates. No evidence of carditis. Recovery from the time of tonsillectomy. Mobilization with a high E.S.R. without ill-effect judged by the weight gain, hæmoglobin rise and E.S.R. fall. Theoretical correction of E.S.R. for anæmia fallacious. Actual correction showed an E.S.R. within normal limits. M. S., female, aged 13 years. Fever and joint pain one week after tonsillitis.

In this case we endeavoured to correct the E.S.R. for anæmia using both Whitby and Hynes', and Wintrobe's correction charts, but there was no marked alteration. When, however, we corrected to a standard hæmatocrit by removal of plasma, we got an E.S.R. within normal range and subsequently it returned completely to normal. The chart illustrates well that patients, particularly adolescent girls, should not be kept at rest solely because of a high E.S.R. in the absence of other signs of activity since mobilization in this case actually produced the fall towards normal of the apparently abnormal reactions.

Another criterion which has been proposed by Taran is the corrected QT interval,— $\sqrt{\frac{QT}{R\text{-}R}}$ and Abrahams (1949) has undertaken a preliminary investigation of our cases from this point of view.

In many cases of carditis we have found that the QT_c falls from its initial abnormal levels to normal during recovery parallel with the E.S.R. When children with a QT_c above the normal upper limit of 0·43 sec. but with a normal E.S.R. are got up, the E.S.R. may rise and although we do not know whether this indicates increased rheumatic activity and cardiac damage or merely a non-specific serological change, we feel it is wise to act as though the former were happening and we therefore put the child back to bed. Fig. 3, however, shows that some children may be got up with markedly abnormal QT_c without ill-effects and we think that such exceptions underline our general attitude at Taplow that no one test is adequate as a criterion.

May Wilson (1940) places high value on the vital capacity. Fig. 4 shows that this does

FIG. 4.—Chart showing congestive heart failure with rheumatic activity. As soon as activity subsided (judged by E.S.R. fall) the patient came out of heart failure (judged by J. V. P.) and the weight and vital capacity rose. Mobilization at the 70th week to Grade 4 and then successfully to Grades 5, 6 and 7 without incident.

FIG. 3.—Mobilization from Grades 4 to 7 (out of bed, walking, etc., to full activity) in the presence of increased QT_c and normal E.S.R. without effect on recovery judged by clinical signs, weight increase and E.S.R. Two temporary setbacks due to tonsillectomy and glandular fever.

coincide very well with other criteria but it is of value chiefly in patients who are recovering from congestive failure. Gain of weight due to putting on flesh, and not due to acute episodes of congestive failure with water retention, is perhaps the least fallible of all these criteria but the change is a comparatively slow one. A well-sustained rise in weight, however, is a very good indication in children that the rheumatic process is over.

In summary, therefore, we feel that bed rest should be maintained until most or all of the criteria we are using (amongst which the most useful are sedimentation rate and electrocardiographic change) are normal and then the patient should be gradually mobilized and a close watch kept on these signs of activity. This applies more to children than to adults in whom cardiac damage is less frequent and who seem to bear a much earlier mobilization with impunity.

Ward Routine

General ward routine is designed to guard against cross infection. New cases are isolated until they are proven to be free from hæmolytic streptococcal infection: a weekly nose and throat swab is taken from all patients and all staff, carriers being isolated, organisms grouped and typed, and persistent carriers sterilized with penicillin. Oiling of the floor and bedclothes has been advocated to cut down cross infection but we have had no personal experience of this. Massell, Dow and Jones have recently claimed that rheumatic fever recurrences following hæmolytic streptococcal sore throat have been cut down from about 50% to nil in a small series of 15 cases treated with penicillin immediately after discovery of the sore throat. This seems theoretically possible since cases thus treated show a very much smaller antibody rise but it depends upon the length of time the infection takes to produce symptoms. We have found that in one case prompt treatment with very large dosage within a few hours of the first tickling of the throat was not sufficient to prevent a severe rheumatic recurrence. It may turn out, however, that the majority of cases can be thus treated in time and if so this is very important indeed.

Salicylates

We come now to "specific" therapy and the salicylate problem. Salicylates although used now for nearly three-quarters of a century are still a controversial subject, and a great deal of argument still occurs as to their action. Despite Coburn's claim that blood levels above 35 mg.% "cure" rheumatic fever, we believe rather that it does little more than relieve the symptoms and mask the evidence of activity. It has been shown at this serum level to depress the E.S.R. in non-rheumatic subjects as well as in rheumatic subjects (Harris, 1947). It decreases fever (in other conditions as well as in rheumatism) and it relieves the pain of joint lesions, but other signs of joint involvement, such as the skin temperature (according

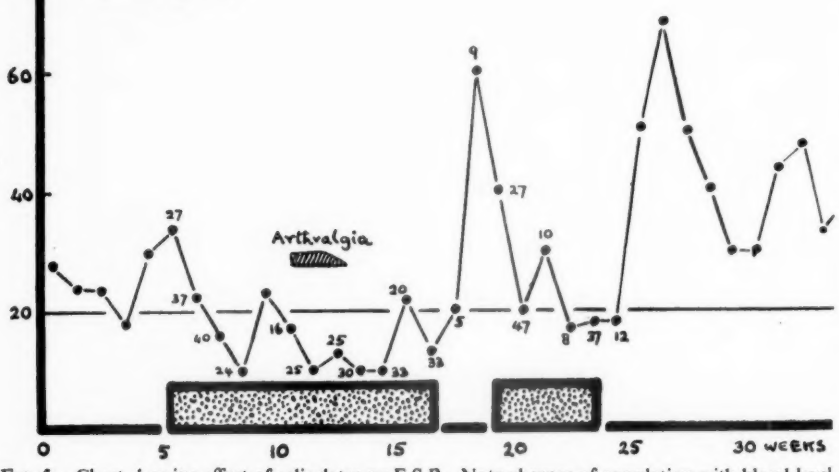


FIG. 5.—Chart showing effect of salicylates on E.S.R. Note absence of correlation with blood level. (Read blood levels in mg.% across chart.)

to Murphy, 1945) and the effusions frequently persist. On both these counts, that is pain and fever relief, salicylates are invaluable in treatment and the lessening of the fever must reduce the work of the heart. If, however, a course of salicylates is interrupted the E.S.R. will frequently rise to its preceding high level (Fig. 5) and indeed we have seen chorea, pericarditis and nodules occur during salicylate treatment as also have others. Furthermore in the severe and active cases with heart failure, salicylate will not arrest the fatal termination. Its toxicity is in some cases a drawback although seldom very severe. Apart from the rare sensitivity reaction with puffy eyes, &c., it produces a respiratory alkalosis due to direct stimulation of the respiratory centre with a secondary depression of CO_2 combining power. It is a mistake to treat this lowered alkali reserve with alkali as it may raise the blood pH still further and precipitate a bad alkalosis. It may produce an alarming but luckily transient psychotic state. Bleeding due to prothrombin depression is seldom seen and is said to be relieved by vitamin K (1 mg. of the synthetic product is equivalent to 1 gramme of salicylate). We have debated whether salicylate bleeding in the basal areas of the brain might be responsible for the occasional hyperpyrexia against which continued salicylates seem ineffective and which should be treated by tepid baths. Recently Meyer and Ragan have reported that sodium gentisate, a breakdown product of salicylates, is just as effective and less toxic. There should be a future for such a drug.

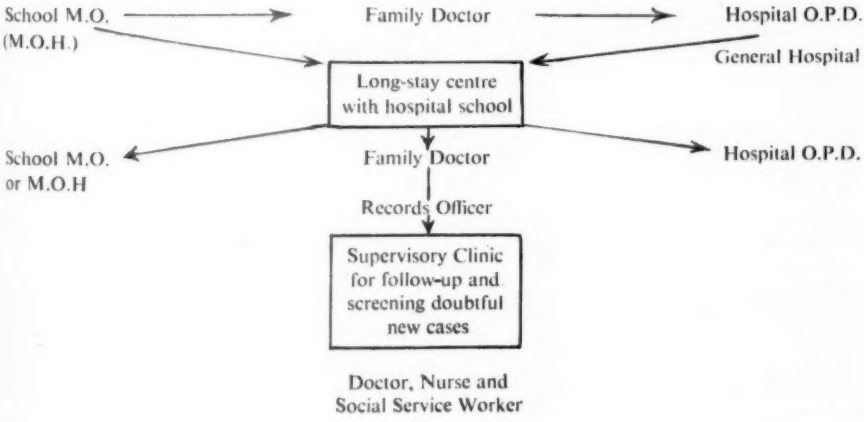
The most spectacular advance in this field is the use of cortisone and ACTH by Hench, Kendall and their colleagues from the Mayo Clinic. ACTH from pig pituitary and cortisone from bile, primarily used in rheumatoid arthritis, have been found by Hench equally successful with rheumatic fever. The QT_c interval, calculated from his data, together with other criteria of activity, shows a decrease within a period of ten days. I have seen other cases treated with ACTH at the House of the Good Samaritan in Boston by Thorn, Massell and Forsham with remarkable improvement but as one of their colleagues remarked: "It seems nearly as good as aspirin, but a bit more expensive." The assessment of its value is much more difficult than in rheumatoid arthritis since rheumatic attacks may be spontaneously terminated within a comparatively short time and it will need a more detailed and critical selection of cases to prove this point if reliance is to be placed on individual case records rather than on statistically controlled investigation which, at the moment, supplies of the substance do not allow. Ultimately it may prove that such hormone treatment is more useful in rheumatic fever than in rheumatoid arthritis since it does not need to be continued for a period of many years.

As in rheumatoid arthritis, there is no evidence in rheumatic fever of a primary hypothalamic, pituitary or adrenal deficiency since the response to adrenaline is normal and we are left with the hypothesis that there is an acquired connective tissue disorder on which the hormones act.

After-care

The management of rheumatic fever involves the care of the child after leaving hospital. The London County Council have been pioneers in this respect and we have adopted their system of supervisory or advisory clinics for looking after the health of the child and of its family following discharge from hospital.

TABLE III



The groundwork for this is laid by getting to know the parents while the child is still in the hospital. It is important also to see that harmonious contact is maintained with the responsible School Medical Officer, the family doctor and the referring hospital. We send copies of the in-patient summary with recommendations regarding physical activity, school, &c., to each of these authorities. This supervision should continue certainly during the next two or three years and preferably through adolescence, since May Wilson has shown clearly that the risk of recurrences is greatest within a short period of the last attack and in the age-group up to 15 (Wilson and Lubschez, 1944). General instruction on avoidance of exposure to infection, damp, chills, and limitation of physical activity if necessary, on school arrangements, housing problems, re-employment for the older children, are all given at this level. It is in the prevention of further recurrences that the co-ordination of the social and the health services is so necessary: and it is in this after-period that the problem of chemo-prophylaxis becomes so important.

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Oral Penicillin in the Prophylaxis of Streptococcal Infection and Rheumatic Relapse

By J. A. PITT EVANS, M.B., B.S.

INTRODUCTION

THIS is a preliminary report of an investigation into the value of penicillin in the prevention of streptococcal infections among children in a Home for convalescent rheumatic fever patients. The work was carried out by a team of laboratory and clinical workers under the direction of Professor Robert Cruickshank.

American, and more recently Australian, workers have found that small doses of sulphonamide (1 to 2 grammes daily) have a prophylactic effect on the occurrence of rheumatic fever relapses by preventing the occurrence of streptococcal infection which is a common precursor of such relapses. However, sulphonamide given over a long period, even in small doses, may produce toxic effects including granulopenia so that some laboratory control, e.g. weekly blood counts, is commonly recommended with prolonged administration. This prophylactic method is therefore unsuitable for most Convalescent Homes where laboratory facilities are poor, and more so for domiciliary practice. There is the added risk of producing sulphonamide-resistant strains of hæmolytic streptococci.

Penicillin is practically devoid of toxicity and is particularly active against the hæmolytic streptococcus which does not readily become drug resistant. Ordinarily penicillin is given by injection but such a method would be quite unsuitable for prolonged use. There is evidence that penicillin given by mouth on an empty stomach is absorbed (if rather irregularly) and that about five times the amount of an intramuscular dose is required to give equivalent blood levels. We therefore decided to try the effect of one daily dose of 100,000 units of penicillin given in 5% glucose (which encourages absorption) before breakfast. Such a dose should with most cases give a maximum blood level of 0·4 to 0·5 unit of penicillin and maintain a bactericidal level against the hæmolytic streptococci for two to three hours.

Children of 5–13 years of age are admitted to the Lancing Convalescent Home for a maximum stay of six months so that they can be followed only for a short period after the attack. However, Wilson and Lubschez have shown that the highest incidence of rheumatic relapses occurs in the first year after an attack and in the age-groups 5–13 years. It might therefore be expected that a number of relapses would occur among the children during their stay in the Home, and this was strongly supported by an analysis of the earlier records. Our main objective, however, was to study the effect of prophylactic penicillin on clinical and latent streptococcal infections among these children.

Details of Scheme

The scheme was started on November 9, 1946, and continued until September 30, 1948, and was carried out at the Children's Heart Home, Lancing, which caters for rheumatic fever convalescents, recruited from a wide area. On admission each child was allocated by random sampling to penicillin or control group. Subdivisions into the sexes and two age-groups 5–8 and 8–13 were made. The treated and control groups mixed freely throughout the scheme.

The penicillin group received 100,000 units of calcium penicillin in ½ oz. of 5% glucose three-quarters of an hour before breakfast. The control group received nothing. No toxic reactions or ill effects from the penicillin were reported during the two years' study.

The clinical side of the investigation was under the charge of Dr. Whiting, the local practitioner, with periodic visits from Dr. MacCarthy whose opinion as to what constituted clinical evidence of fresh rheumatic activity has been taken as final. These included joint swellings, or joint pains with limitation of movement, erythema marginatum, pericarditis, carditis, and subcutaneous nodules; most of these manifestations to be accompanied by rise of temperature and tachycardia.

The laboratory side of the investigation was my responsibility and was as follows:

(*a*) Weekly nose and throat swabs were collected from the children and plated out on the same day at the beginning of the scheme and after overnight refrigeration during the second half of the investigation; all hæmolytic streptococci were grouped and typed.

(*b*) Approximately once a month all children had a venepuncture and the sedimentation rate and anti-streptolysin O-titre estimated. The diagnosis of streptococcal infection required the isolation of Lancefield group A hæmolytic streptococci and as a rule a two-tube or more rise in the anti-streptolysin O-titre.

During the twenty-three months of the investigation, 155 children received penicillin and 145 acted as the control group.

The results have been analysed to compare (1) the incidence of hæmolytic streptococcal carriers in the two groups; (2) the incidence of clinical streptococcal infection; and (3) the occurrence of rheumatic relapses or evidence of fresh rheumatic activity.

Table I shows the incidence and duration of streptococcal carriers in the two groups with ratios of approximately 4 : 1 in favour of the penicillin group. It should be noted that

Table I.—All Children in the Survey: Incidence of Streptococcal Carriers

	Penicillin	Control
Total No. of patients	155	145
No. of patient-weeks in home	3,345	3,248
Average length of stay in weeks	21·6	22·4
No. of patient-weeks H.S.* carried in throat	71	242
No. carrying H.S.* in throat for two consecutive weeks	7	33
No. carrying H.S.* in throat for 3 consecutive weeks	4	17

*Group A hæmolytic streptococci.

the two groups are approximately equal as regards the number of cases and the length of time that they were in the Home.

Table II shows the incidence of clinical streptococcal pharyngitis or tonsillitis in the two groups. *In the penicillin series*, the one doubtful case was a girl with chronic tonsillar infection with occasional exacerbations. *In the control group* there were 7 definite cases of tonsillitis due to Lancefield group A streptococci: in 6 of these cases there was a rise in the anti-

TABLE II.—CLINICAL STREPTOCOCCAL PHARYNGITIS

Penicillin group	Control group
1 doubtful case (H.S. + No rise of A.S.O.)	7 definite cases with H.S. (group A) (Rise of A.S.O.* in 6 cases) 2 doubtful cases (H.S. negative. Rise of A.S.O.)

*A.S.O. = anti-streptolysin O-titre.

streptolysin titre, and in 5 the E.S.R. was also increased. The two doubtful cases had typical infections with rise of A.S.O. but hæmolytic streptococci were not isolated from their throats during the acute stage. One of these patients had been given sulphonamides at onset and this may have eliminated the hæmolytic streptococci. There were two other clinical cases without hæmolytic streptococci or rise of A.S.O.

As far as rheumatic relapses are concerned, there were none in the penicillin group and 4 cases in the control group. Graphs were shown to illustrate the main laboratory findings in 3 of these cases.

The evidence therefore indicates that a daily dose of 100,000 units of penicillin given orally on an empty stomach has considerable value as a prophylactic against streptococcal infection and consequently rheumatic relapses among rheumatic children in a Convalescent Home.

[*November* 22, 1949]

Pulmonary Changes in the Reticuloses

By NEVILLE OSWALD, F.R.C.P.

IT is to be expected that the lungs, with their abundance of reticulo-endothelial cells and rich blood supply, will often be affected in such general disorders as the reticuloses. Lymph glands may enlarge; those in the mediastinum may cause pressure on veins resulting in pulmonary œdema and pleural effusions; pressure on bronchi may lead to atelectasis; the broncho-pulmonary glands, which are situated at the bifurcations of bronchi as far out as their third divisions, may give rise to masses within the substance of the lungs; any of these glands may be unable to contain actively proliferating reticuloses, which may penetrate their capsules and invade the adjacent pulmonary parenchyma. The peripheral parts of the lungs may be the site of infiltrations which have a wide range of radiological appearances; they may be diffuse from capillary exudation, finely nodular from proliferation in the lymphoid follicles or even miliary; there may be roundish masses as a result of blood-borne metastases from the more malignant types of reticulosis, such as lymphosarcoma. Vascular changes are common in the acute and subacute reticuloses; masses of abnormal cells are often seen blocking the capillaries and smaller blood vessels leading to thrombosis, and infarction is one of the chief causes of pulmonary consolidation. Capillary hæmorrhages may occur as a result of pulmonary congestion and abnormalities in the circulating blood. Pulmonary cavitation is unusual; it may take the form of a lung abscess complicating pneumonia or infarction, or there may be an associated pulmonary tuberculosis; occasionally lymphadenomatous glands break down, whether or not they have been treated by irradiation. Last, there are non-specific infections, which particularly have to be remembered in acute leukæmia where there is inflammation and ulceration in the upper part of the respiratory tract; bronchopneumonia frequently develops as a terminal event.

These changes are to a large extent characteristic of the reticuloses in general, most of them having been described at some time or other in the individual diseases.

Hodgkin's disease.—Rather more than one-half of all cases show abnormal radiographs of the chest, usually in the form of enlarged mediastinal glands or, less frequently, pleural effusions. Roughly one in ten shows changes in the lungs themselves. This last group can conveniently be divided into four.

(*a*) Involvement of glands: It is evident, either on radiological or pathological evidence, that the lymph glands can most conveniently be divided into the paratracheal, tracheo-

bronchial and broncho-pulmonary groups. The tracheo-bronchial glands in the region of the bifurcation of the trachea are most commonly affected and the lymphadenomatous infiltration often extends upwards and downwards to involve all three groups (Fig. 1).

(*b*) Pressure effects of enlarged glands: This may lead to collapse of lung, œdema and pleural effusion (Fig. 2).

(*c*) Roundish masses in the substance of the lungs which are clearly beyond the bounds of the broncho-pulmonary glands and usually represent blood-borne metastases (Fig. 3).

(*d*) Parenchymal infiltration, which shows great variation in extent and distribution and resembles pulmonary tuberculosis (Fig. 4).



FIG. 1.—Widespread infiltration of glands in Hodgkin's disease.

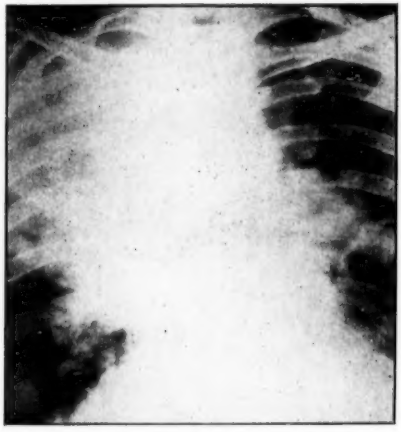


FIG. 2.—Collapse and consolidation of the upper lobe in Hodgkin's disease.

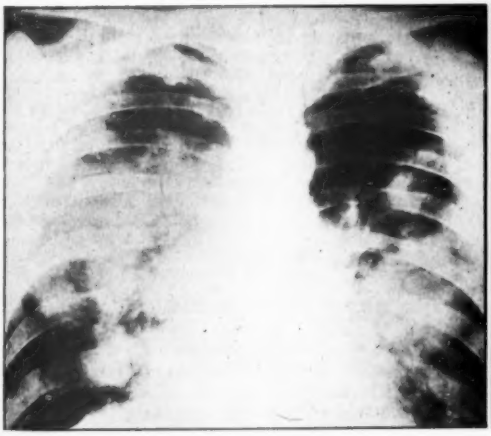


FIG. 3.—Roundish masses in the periphery of the lungs in a case of Hodgkin's disease which underwent sarcomatous degeneration.

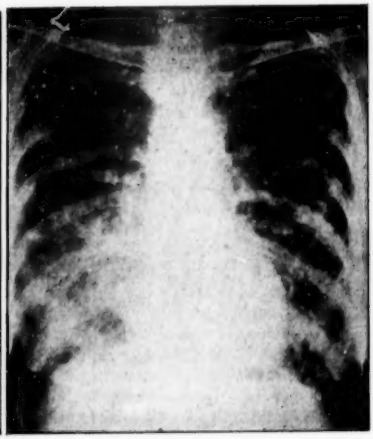


FIG. 4.—Widespread infiltration of the lungs in Hodgkin's disease without radiological evidence of glandular involvement.

Closely related to lymphadenoma is that triad of diseases, *lymphosarcoma*, *lymphatic leukæmia* and *mycosis fungoides*. Abnormal radiographs of the chest occur about one in five, again mainly in the form of enlarged mediastinal glands or pleural effusions. When the lungs themselves are invaded, the radiological appearances are indistinguishable from each other or from Hodgkin's disease, though the rate of progress in the latter tends to be rather slower.

A lady of 57 gave a six-years' history of progressive skin lesions which were proved, on biopsy, to be mycosis fungoides. Three months before death her lesions appeared to be limited to the skin and a radiograph of her chest showed no abnormality. During the last two months of her life she rapidly went downhill and a further film showed rounded masses in both lungs (Fig. 5).

Autopsy revealed similar masses in the liver, thyroid and œsophagus. The sudden terminal dissemination of mycosis fungoides is by no means unusual, even after a great number of years; the lungs are often affected, usually in the form of multiple rounded deposits.

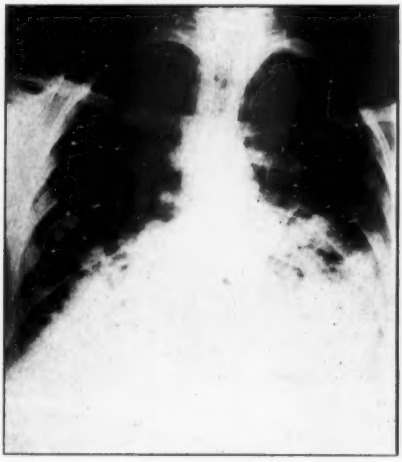


FIG. 5.—Pulmonary involvement in mycosis fungoides.



FIG. 6.—Nodular infiltration in chronic myeloid leukæmia.

The pulmonary changes in *chronic myeloid leukæmia* are usually slight and inconclusive. Occasionally there are somewhat enlarged mediastinal glands and rarely there is a diffuse infiltration of the lungs with fibrosis and infarction.

A man of 57 had suffered for several years from a generalized rash which had been diagnosed as pityriasis lichenoides, a diagnosis which, I am informed, is used in cases of doubt to indicate a condition of uncertain ætiology. For three years he suffered from increasing breathlessness and bronchitis, during which he had two prolonged attacks of bronchopneumonia. Radiographs showed a nodular type of proliferation of lymph follicles similar to that seen in silicosis and sarcoidosis (Fig. 6). His blood count showed 88,000 white cells, almost all of which were of the myeloid series. Autopsy revealed a typical myeloid leukæmia of the marrow, spleen, liver and lymph glands. The lungs showed a generalized fibrosis together with aggregations of myeloid cells in the lymph follicles and peribronchial lymphatics, together with thrombosis in the smaller blood vessels.

In *acute leukæmia* about one-third of all cases, particularly the monocytic variety, have acute inflammatory lesions in the upper respiratory tract. Pulmonary lesions are often dramatic and comprise pneumonia, infarction, œdema and the outpouring of immature cells. Pathological interpretation is often difficult as the white cells in the lungs are the same as those in the blood. Partial and complete thromboses are very common and most of the larger lesions in cases in the literature are considered to have started as infarcts. These occasionally break down and form cavities which often give little in the way of symptoms.

A man aged 48 developed acute monoblastic leukæmia. He had a sudden onset of pneumonia which never appeared to resolve satisfactorily. A month later he developed ulceration of his throat and gums with enlarged glands in the neck which persisted. His general condition steadily deteriorated and he died six months after the onset of symptoms. His white blood-count varied from 4,000 to

100,000 and usually contained about 70% of blast cells and monocytes. A radiograph showed bilateral lesions which resembled tuberculosis, but consisted of consolidation secondary to infarction as proved at autopsy (Fig. 7). The liver, spleen and lymph glands showed a typical monoblastic reaction.

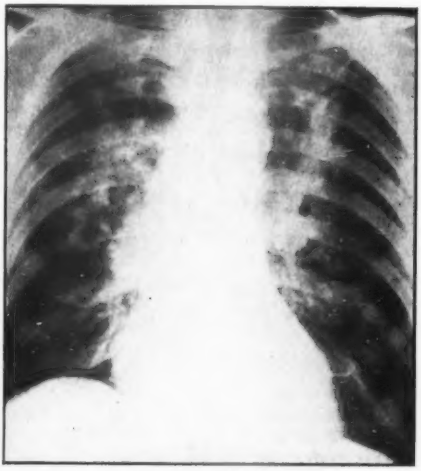


FIG. 7.—Infarction in both lungs in acute monoblastic leukæmia.

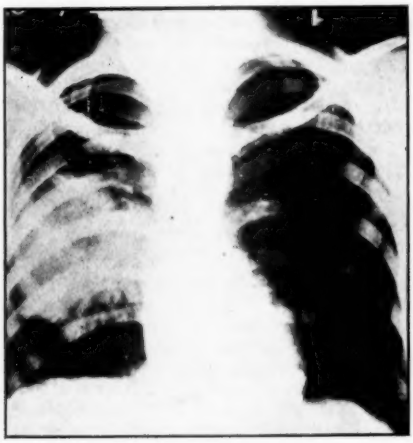


FIG. 8.—Pneumonia with abscess formation in acute myeloblastic leukæmia.

A boy aged 14 was admitted to hospital suffering from acute myeloblastic leukæmia. His illness started with septic lesions of his fingers which failed to heal, lassitude, sore throat with ulceration and enlarged glands in the neck. He died after progressive emaciation at the end of six months. His white blood counts were in the region of 200,000 with an average of 90% of primitive myeloid cells. One month before death he developed an irritating cough and rise in temperature which coincided with an increase in the ulceration of his mouth. His pulmonary symptoms were slight and a film of his chest two months previously had shown no abnormality. Radiographs now showed a roundish lesion with a cavity in the centre in his right midzone (Fig. 8). Autopsy revealed a mass of consolidation in the dorsal segment of his right lower lobe with a subacute abscess cavity in the centre. There was no evidence of tuberculosis or infarction. In view of the oral sepsis and the site and behaviour of the consolidation, an aspiration pneumonia with subsequent breakdown is the obvious explanation. The bone-marrow, liver, spleen and lymph glands showed the characteristic changes of acute myeloblastic leukæmia.

We now come to a group of diseases which are related to *disorders in lipoid metabolism.* In Gaucher's disease, which usually runs a prolonged course, pulmonary involvement is rare. Myers (1937) reported a case of considerable mediastinal glandular enlargement with dense shadows radiating out from the hila almost to the periphery of the lungs; at autopsy the lungs and mediastinal glands were packed with Gaucher's cells. Merklen *et al.* (1933) repeatedly found Gaucher's cells in the sputum of an advanced case.

In Niemann-Pick's disease, which is uniformly fatal before the age of 3, there may be an outpouring of large pale cells into the lungs as part of the general disease process. Canmann (1944) reports a case in which many of the alveoli were packed with such cells. Apart from œdema and congestion there are no characteristic pulmonary changes.

Next there are three conditions which appear to be varieties, or even stages, of the same disease. First there is the Letterer-Siwe disease which is an acute aleukæmic reticulosis of infants, giving rise to fever, anæmia, enlarged liver, spleen and lymph glands, which ends fatally in a few months and has as its characteristic cell a large non-lipoid-containing mononuclear. Secondly there is Hand-Schüller-Christian disease with its classic triad of exophthalmos, diabetes insipidus and erosions of the skull which is less rapidly fatal, usually affects children and is associated with the proliferation of large mononuclear cells containing cholesterol. The third condition has been termed eosinophilic granuloma of bone

(Lichtenstein and Jaffe, 1940); large bony erosions occur which resemble cysts and contain masses of eosinophilic cells. There may be an increase of eosinophils in the other organs which contain reticulo-endothelial cells and in the blood; older children are commonly affected and the disease in a pure form may run a chronic course. Post-mortem examination often shows a mixture of two, or even all three of these diseases. So far as the lungs are concerned, the changes are very similar regardless of which predominates elsewhere, and are quite different from anything seen in any of the other diseases of the reticulo-endothelial system. The lesions are diffuse throughout both lungs. In the early stages there would appear to be a proliferation of reticulo-endothelial cells which soon gives place to a generalized granulomatous infiltration; this in turn may lead to fibrosis and cyst formation, giving a honeycomb appearance. Microscopically, there is a mixture of inflammatory cells, eosinophils and, sometimes, the characteristic large mononuclears which may contain lipoid. Thannhauser (1940), and more recently Parkinson (1949), use the rather unwieldy term "eosinophilic xanthomatous granuloma" to embrace all these changes; this has the advantage of describing such pulmonary changes when evidence elsewhere in the body of one of these diseases is not forthcoming; also, it is usually impossible, on examination of the lungs alone, to tell with which disease one is dealing since the large mononuclear cells are usually scanty, as a result of secondary infection, by the time death occurs.

Finally we come to the *leukæmoid states* in which there is a leucocytosis with immature cells in association with some entirely different disease. Such patients are usually ill and the presence of acute leukæmia has to be proved or excluded. The liver, spleen and lymph glands may be enlarged, but on section show none of the typical histological changes of a leukæmia. Forkner (1938) stresses two points in clinical differentiation, namely that in acute leukæmia there is nearly always a marked decrease in the number of blood platelets, and that almost constantly there are at least 70% and usually 80% of white cells of a uniform and immature type, neither of which features is often seen in leukæmoid states. Amongst the pulmonary conditions which may provoke this response, we are all familiar with pneumonia in infants and young children, in whom such a leucocytosis is quite common. Whooping cough, which normally produces a relative lymphocytosis, may lead to a rise in white cells to 100,000 or even 200,000 per cubic millimetre nearly all of which are lymphocytes; cases recorded with these high figures have nearly always been complicated by bronchopneumonia.

Pulmonary tuberculosis may be associated with a leukæmoid response, which is usually of the myelogenous type. It is an unwelcome sign, the majority of recorded cases having died from miliary tuberculosis within a few months of discovery of the abnormal blood picture.

A carpenter aged 25 was admitted to hospital with one week's history of lassitude, cough and breathlessness, his wife having died from pulmonary tuberculosis some four months previously. On admission, his temperature was 102° and a radiograph of his chest showed infiltration of the left lung with a moderate-sized pleural effusion. His effusion rapidly increased and several pints of turbid amber fluid were aspirated, from which one atypical acid-fast bacillus was isolated. His sputum contained tubercle bacilli. He rapidly went downhill in hospital with high fever and died six weeks later.

Autopsy revealed scattered nodules of caseous bronchopneumonia in both lungs with a superimposed miliary tuberculosis. The mediastinal lymph glands were enlarged and caseous. The liver, spleen and kidneys were riddled with miliary tubercles.

The post-mortem appearances suggest that he died from an overwhelming primary infection, there being a severe primary complex in the chest which gave rise to a miliary dissemination. A chart of his blood picture (Table I) shows weekly blood counts during

TABLE I.—LEUKÆMOID REACTION DURING A TERMINAL MILIARY DISSEMINATION IN A CASE OF ACUTE PULMONARY TUBERCULOSIS

		Oct. 17	Oct. 29	Nov. 5	Nov. 12	Nov. 17	Nov. 23	Dec. 1
Total W.B.C.	..	32,000	68,000	82,000	36,000	17,000	8,000	15,000
% Myeloblasts	..	2·5	2	1	3	1	—	1
% Myelocytes	..	32·5	28	42	10	12	7	13
% Polys.	..	46	58	50	65	75	81	77
% Eosinos.	..	—	—	1	12	—	—	—
% Lymphos.	..	12·5	5	5	7	10	9	8
% Monos.	..	6·5	7	1	3	2	3	1

Admitted—October 15. Died—December 1.

his stay in hospital. It will be noted that there were never as many as 70% of cells of a uniform and immature type, and that the last three blood-counts approached normal figures. In addition, there was no change in the spleen or lymph glands at autopsy to suggest a leukæmia.

The whole subject of the leukæmoid reaction is a difficult one, and there would seem sometimes to be no strict dividing line hæmatologically between it and the leukæmias. As an additional complication, leukæmic patients are prone to develop pulmonary tuberculosis.

I would like to thank Drs. Maurice Davidson, E. R. Cullinan, R. Bodley Scott, J. G. Scadding and R. M. B. MacKenna for allowing me to record their cases.

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A Ten-Year Follow-up of Peptic Ulcer Cases with Special Reference to Results of Medical Treatment [*Abstract*]

By LAURENCE MARTIN, M.D., F.R.C.P.
Addenbrooke's Hospital, Cambridge

356 proven cases of peptic ulceration which had been admitted as in-patients to Addenbrooke's Hospital during the years 1934–38 inclusive were followed up in 1948–49. Of the total, 142 had died, 195 were traced, and 19 were untraced. Of those traced 96 gastric and 43 duodenal ulcer cases had been treated by medical means alone with or without the simple suture of a perforation. At follow-up 42 (44%) of the 96 gastric and 14 (32·5%) of the 43 duodenal ulcer cases were inactive and had been free from symptoms for the previous five years. After full enquiry into the regimen of treatment which had been followed by each patient during the follow-up interval it was concluded that medical treatment had not influenced the natural course of the peptic ulcers. For a full account of the whole survey *see* Martin, L., and Lewis, N. (1949) *Lancet* (ii), 1115.

The Respiratory Factor in Ankylosing Spondylitis

By F. DUDLEY HART, M.D., F.R.C.P.

Middle-aged man; complaining of breathlessness on exertion. After X-ray examinations and investigations he was diagnosed as a case of emphysema. But on his third attendance at hospital he was correctly diagnosed by an assistant, who had also worked in the Rheumatism Clinic, as a case of ankylosing spondylitis.

History.—In the trenches in the first World War in 1916 when a young man in the early twenties, the sudden onset of severe low backache led eventually to his discharge from the Army as a case of fibrositis of the back in a man of poor moral fibre. Since then backache and spinal stiffness relapsed and remitted, with the condition gradually worsening until he was seen by us thirty-three years after the onset of the condition. It was at this time that the diagnosis of ankylosing spondylitis was first made. His fixed, bent back and chest expansion of ½ in. made a typical picture.

Ankylosing spondylitis starts insidiously, usually in the lower spine, and the sacro-iliac joints are early affected. Nevertheless, by the time the patient comes to hospital, there is usually limitation of thoracic expansion, measurements of chest expansion at nipple level being reduced to 1 in. or less, the vital capacity significantly reduced by 20–40% of the normal figure for that subject. In a recent enquiry at Westminster Hospital it was found that of 62 patients with ankylosing spondylitis, 46 (74%) had experienced tightness and discomfort in the chest wall on deep inspiration at some time after the onset of the disease. Only 8 (13%) had never experienced these symptoms at any time since the onset of their spinal condition. 8 (13%) had noticed these symptoms only slightly and intermittently. In a few cases these symptoms dominated the picture from the first. In the cases we have seen there has been significant reduction in chest expansion in 3 out of 5 patients in cases of duration

varying from a few months to thirty-three years. It is not a late finding only, it is usually present at the patient's first attendance at our Clinic.

Underlying pathology.—Every thoracic vertebra has eight articular facets—intervertebral superior and inferior right and left, costo-vertebral and costo-transverse (Fig. 1). All these may be affected, though commonly the involvement is a patchy and irregular one. The result is pain and limitation of costal movement in the earlier stages, complete fixity with bony fusion in the late stages of advanced cases (Figs. 2 and 3). Respiration is largely diaphragmatic (Figs. 4, 5 and 6). The patient complains of stiffness and immobility of the chest wall, inability to take a deep breath, and not infrequently tenderness in sternum and/or ribs. This last complaint was present at some stage in two-thirds of our 62 patients. Inflammatory changes in the spine may be referred to points lower in the chest or to the flanks and abdomen, simulating the girdle pains of other diseases. Exertional dyspnœa may be caused, though other factors, e.g. hip involvement, may limit exercise capacity and render exertional dyspnœa unlikely, or impossible. It is not uncommon for thoracocervical kyphosis to give a hang-dog appearance to these patients, but this factor is absent in many, and probably does not affect vital capacity greatly unless this deformity is marked. In 7 normal students Dr. Keith Robinson found little effect on vital capacity by taking estimations in equivalent positions of kyphosis (Table I). Such deformity, if marked, will certainly play a part in restricting thoracic movements and diminishing vital capacity, but this factor probably is not an important one in the average case as compared with involvement of rib or intervertebral articulations.

TABLE I

Subject	Vit. cap. in c.c.	90 degrees flexion of trunk	Full cervico-dorsal flexion	Half-way position
J. B.	5,300	5,200—98%	4,600—87%	5,000—94%
A. D.	5,000	4,900—98%	4,000—80%	4,300—86%
P. G.	4,400	4,200—96%	3,800—87%	4,100—93%
H. C.	5,200	5,200—100%	4,400—85%	
J. B.	3,800	3,800—100%	3,200—84%	
D. D.	4,300	4,100—95%	3,600—84%	3,800—88%
A. B.	5,500	5,400—98%	4,500—82%	5,100—93%

Thoracic pain may be a striking symptom in this disease. One man, 37 years of age, was admitted to hospital with a five months' history of aches, pains, stiffness in the lower thoracic spine and across the shoulders. Two months after the onset of these symptoms lumbar pains and stiffness of the back made their appearance, together with a tight constricted feeling in the chest. He felt he could not fill his lungs properly. He was admitted to hospital in great pain, unable to bend his back at all or lie comfortably in bed in any position, and he was unable to take deep inspiratory efforts because of the severe painful constricted sensation in the chest wall. Analgesics gave only partial and temporary relief. Chest expansion was under 1 in. at nipple level, vital capacity 56% of normal. On deep X-ray therapy to the spine, 1,200 r to three ports, the pain abated. Improvement was noted after the second application to each field. After the completion of the course vital capacity had risen to 80% of normal; a few months later to 110% of normal, his chest expansion to 3 in. A second case, a man aged 50, was admitted with pyrexia and severe constricting pain in the chest of four months' duration. He had a history of backache going back four years. The same picture of painful restlessness with inability to find a comfortable position in bed was noted, the combination of stiffness, pain and constricted thoracic sensation producing marked distress and making nursing very difficult. X-rays showed a more advanced spinal condition than in the first case, but relief of the severe symptoms was obtained within seven days of the start of deep X-ray therapy.

In such severe cases with the thoracic discomfort predominating, deep X-ray therapy appears to give greater relief than any other measure.

A third case may be quoted at this point.

A man aged 50, previously well and extremely fit, noticed in August 1948 stiffness of the spine and cough with shortness of breath. Stiffness was most marked in the lumbar region but later involved the neck. He was admitted at this time to a hospital overseas and as he was found to have ankylosing spondylitis was treated on constant bed rest. In October 1948, approximately a month after admission to hospital, sudden onset of pain and dyspnœa occurred due to right-sided spontaneous pneumothorax. Aspiration of air was carried out. As the pneumothorax failed to expand a right phrenic crush was attempted, happily only the sympathetic nerves of the area were avulsed, giving him a right-sided Horner's syndrome and leaving his diaphragm unaffected. He returned to England at the end of the year and came under our care in March 1949. He was a typical spondylitic. There was moderate thoracic kyphosis with the head held rigidly forward. The lumbar spine was flattened and all spinal movements severely restricted. All peripheral joints were normal. He was tender over the last ribs on both sides. His chest expansion was ¼ in. Signs were present of a right pneumothorax. X-rays showed a right pneumothorax with adhesions at the apex; no fluid was present. There was a little old tuberculous infiltration at the left apex. Diaphragmatic movement was full; no rib movement was present. Advanced ankylosing spondylitis was seen in sacro-iliac joints, dorsal and lumbar

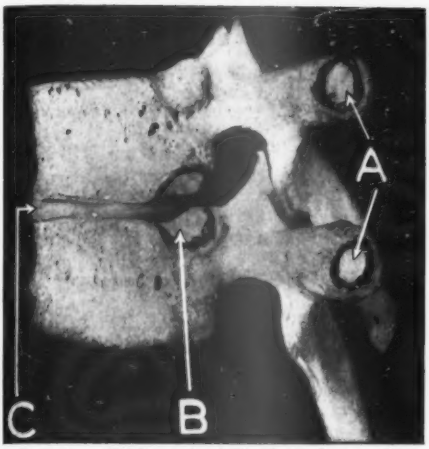


FIG. 1.—Fifth and sixth thoracic vertebræ. A.—Articular facet with ribs. B.—Articular facet of rib with adjacent vertebræ. C.—Intervertebral disc. Involvement of A and B causes pain and fixation of rib on vertebral column.

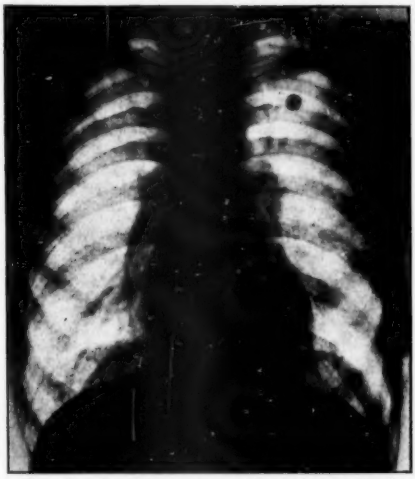


FIG. 6.—Double exposure X-ray in ankylosing spondylitis. Rib movement is slight, diaphragm excursion is normal.



FIG. 2.—Normal costo-transverse articulation with first rib.

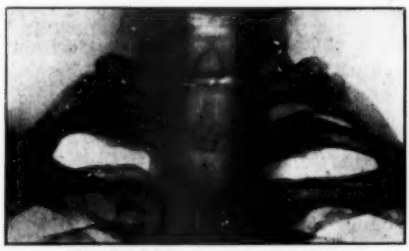


FIG. 3.—The same joint involved in ankylosing spondylitis.



FIG. 4.—Double exposure X-ray in normal subject.



FIG. 5.—Double exposure X-ray in emphysema. Rib movement is not apparent; diaphragmatic excursion minimal.

spines. Vital capacity was 38% (1,700 c.c.). On deep X-ray treatment, accompanied by breathing exercises and the freedom of not only the ward but the entire hospital for the encouragement of full bodily exercise, his spinal condition improved markedly, but the pneumothorax only partially, and now, eight months later, this is still present.

This case-history shows the importance of exercise in general, and breathing exercises in particular. Immobility, particularly in plaster beds or jackets, hastens fusion of the chest wall and lowers the vital capacity markedly, the chest becoming fixed in the position of rest. Advanced cases of ankylosing spondylitis are almost completely dependent on their diaphragm for respiration, and one shudders to think what might have happened had the diaphragm been paralysed in the last case quoted above. If operations are necessary in such cases, the anæsthetist should be fully aware of the dangers, post-operative treatment must be carefully supervised, and early mobility and breathing exercises instituted. Such patients should be the minimum time in bed.

I have had 5 cases of ankylosing spondylitis who had also pulmonary tuberculosis. In each case the spinal condition preceded the pulmonary one. The therapeutic problem is here a difficult one as the two treatments are opposed—rest for the pulmonary tuberculosis, mobility and deep X-rays, postural and breathing exercises for the spondylitis. The maximum mobility possible should be allowed such patients, who on resting feel their spinal condition worsening in fixity, pain and forward curvature. Every effort should be made to prevent spinal deformity by correct posturing; the patient should not be allowed to become bent forward on a pile of pillows. Some substance, such as ACTH or Compound E (Kendall) (Cortisone), known to be effective in ankylosing spondylitis, may help in such difficult cases in the future; at present the combination of the two diseases is a therapeutic nightmare.

In 62 cases of ankylosing spondylitis we have enquired as to increasing incidence of coughs, colds and respiratory complaints. This enquiry has not revealed any particular predisposition to these complaints since onset of the spinal condition.

The symptoms resulting from restricted respiratory movement of the thoracic wall by ankylosing spondylitis are easily distinguishable from the dyspnœa of cardiac or pulmonary disease, the essential differentiating features in ankylosing spondylitis being:

(*a*) Spinal rigidity with absence or diminution of spinal extension.
(*b*) Diminished chest expansion with no physical signs in lungs.
(*c*) Chest is fixed in partial expiration, i.e. the position of rest, rather than partial inspiration as in emphysema or bronchitis.
(*d*) Absence of bronchial spasm and cough.
(*e*) Occasional tenderness on percussion over the sternum, and less commonly the adjacent costal cartilages and the lower ribs.

SUMMARY

Involvement of costo-transverse and costo-vertebral articulations in the rheumatoid process, known as ankylosing spondylitis, causes diminution in chest expansion and thoracic pain, sometimes severe. In the early stages limitation of thoracic expansion is due to pain arising at the costo-vertebral and costo-transverse joints; later bony ankylosis leads to a fixed chest. Spinal rigidity with loss of spinal extension on deep inspiration is a contributing factor. Spinal kyphosis, if extreme, adds to respiratory disability. Thoracic pain and exertional dyspnœa, so caused, may be erroneously attributed to cardiac or pulmonary disease unless other signs of ankylosing spondylitis are noted.

Section of Ophthalmology

President—M. L. HINE, M.D., F.R.C.S.

[*November* 10, 1949]

Recherches Kératoplastiques

By JOHN FOSTER, F.R.C.S. and ARTHUR LISTER, F.R.C.S.

Mr. John Foster:

This title was adopted by my co-author and myself as we planned our tour in France to see as much keratoplasty as possible.

We visited Professor Bonnet at the Hôpital Edouard Herriot at Lyons, 120 of whose 3,000 beds are in an Ophthalmic Pavilion. Some plastic operations and a Lagrange sclerectomy were performed. This latter operation is performed with an almost vertical knife-entry, and the sliver of sclera "sawn off" the conjunctival flap with a Graefe knife. Far from being merely a stage in the development of the trephining operation (as many of us imagine here) it is used in preference to the latter and we saw many excellent results from it.

Our next visit was to the Hôpital de l'Antiquaille, where Professor Paufique has a hundred beds. It was here and in several private hospitals in the city that we were privileged to see the Professor perform, besides other operations, some twenty keratoplasties in a single week. In all these institutions the nursing is carried out by réligieuses. This enormous volume of work is only possible because Paufique's practice is purely pathological, refractions being referred elsewhere.

Theatre Technique.

Intense lighting from a scialytic lamp plus a portable searchlight directed from above and to one side are employed in all cases: black towels are used for contrast.

Complete aseptic technique is employed, the surgeon wearing cap, mask, gown, sterile linen bags over the boots, and linen gloves (rubber is judged too slippery). The patient's hair is restrained by a stockinet cap and the eyebrows as well as the eyelashes are removed. Iodine is applied to the skin and a speculum inserted to ensure thorough irrigation of the fornices during lavage.

Keratoplasty.

In all types of keratoplasty a van Lint akinesia and retrobulbar anæsthesia are employed, 20% of ethyl alchohol being added to the scurocaine. A preliminary iridectomy is performed in all cases with synechiæ, a special operation of Paufique's own devising being employed where an oblique trephining of the cornea permits half the disc to be elevated like a trap-door for detachment of anterior synechiæ from an adherent leucoma.

All these measures are antidotes to post-operative glaucoma which, though less frequent than it was, remains the "curse of the grafting classes".

An Arruga speculum is employed and all grafts are finally held in position by egg membrane and by the cruciform sutures described by Zirm. The membrane is cut from the hard-boiled egg by trephine and preserved in alcohol, being dipped in saline before use and nicked here and there at the edge to make it fit better. If egg membrane is not employed, pressure furrows from sutures may persist up to three months in a lamellar graft and a lesser time in the perforating type.

In keratoconus where the graft and cornea are unequally thick, the membrane may have to be omitted and in large lamellar grafts which do not bed down well, direct edge-to-edge sutures (Grieshaber 81/10 needles and Jayle's conjunctival forceps are required) may be employed. One black silk skin suture is inserted afterwards to hold the lids together for four days.

Several donor eyes are available in each case, so that an imperfect graft can be rejected without hesitation. The whole position in this matter, in France, has been revolutionized by the decree 47.2057 of October 20, 1947, which reads: "When in certain listed hospitals death has been certified by two members of the staff after application of suitable tests and the head of the clinic considers pathological or therapeutic interests require it, post-mortem and removal of organs may be performed in the first twenty-four hours without obtaining the consent of the relatives."

This enactment might serve as a model for Great Britain as the work seen in France clearly shows that lamellar keratoplasty will benefit a large number of cases hitherto regarded as untreatable here. The supply of donor eyes excised for neoplasms will be quite inadequate to meet these new demands.

Lamellar Keratoplasty.

This was not only applied to indolent corneal ulcers and active trachoma, and the dystrophies of Haab-Dimmer and Groenouw but also to aphakic eyes, to Fuchs' epithelial dystrophy and corneæ porcelainized by burns, which can then be subsequently grafted by the penetrating method with some hope of success.

The recipient is first trephined with a Franceschetti trephine of 5–10 mm. diameter set to cut at 0·25 or 0·5 mm. according to the depth at which the opacity is judged to lie. Both surgeon and assistant check the verticality of the trephine simultaneously. When the depth of the trephine cut is judged equal and adequate all round, a small elbowed knife is used to start the undercutting. This is continued by retracting the disc with a small double hook as it is cut from the cornea by a Desmarres' scarificateur. Further layers may be removed to ensure a bed free from scar tissue. In one case the final layer could only be removed from Descemet's membrane after paracentesis (nearer the edge of the cornea) to render it more lax. This was one of the most remarkable pieces of surgical craftsmanship I have ever seen. Hæmorrhage is carefully stopped by touching bleeding points with a cautery heated in a spirit lamp. The graft is not cut until the bed is prepared as only then is the thickness of graft required known. The bed must be dry.

Donor eyes are stored in hour-glass-shaped bottles with a little water in the bottom, at 4° C. up to twelve hours for penetrating grafts and up to seventy-two hours for lamellar grafts.

The assistant, using both hands, holds the eye in gauze on a table while the graft is cut. The technique is similar and the disc of the same size as that taken from the recipient eye. It is then placed in position, after dipping in penicillin, and retained as described above.

Penetrating Grafts.

The graft in this instance is usually cut first, with a 5 mm. Franceschetti trephine. It is then dipped in penicillin and placed aside in dry gauze. The pupil centre of the recipient's eye is marked with Indian ink. The 5·1 mm. trephine has a central point which is placed on this to make the initial cut before inserting the sutures. No attempt is made to cut the disc completely through. As soon as the anterior chamber is entered the disc is drawn up at this point and cut away along the line or the trephine mark by an Arruga knife. This instrument leaves few, if any, Descemet tags and tends to cut a larger rather than a smaller opening so the line must be followed carefully.

The pupil is small at the start of the operation but mydricaine is injected subconjunctivally and the placement of the egg membrane delayed until the pupil has dilated past the edge of the graft. In large (7 mm.) grafts pilocarpine is instilled to draw the pupil away from the edge of the graft in the opposite direction.

Tattooing.

In one case where several grafts had failed (in a case of tuberculous keratitis) a dental syringe was used to inject Chinese ink into the substantia propria overlying the pupil. This produced a round, densely black area. There was no reaction when seen two days later.

Apart from the demonstration of the technical details of lamellar grafting and the wide range of cases to which it could be applied and their after-results, the most impressive lesson we learned was the degree of skill and confidence which a gifted surgeon can attain in this operation, given adequate material.

Although Professor Paufique regards lamellar keratoplasty as more difficult than the penetrating to perform, the greater variety of cases to which it is applicable and the fact that the anterior chamber is not opened should render it immediately popular here, but for the limiting factor of donor material.

Our grateful thanks are due to Professor and Madame Paufique, and his assistant, Dr. Hugonnier.

Mr. Arthur Lister

From Lyons we went to Nantes where we spent four days watching the work of Professor Gabriel-Pierre Sourdille. He has some 140 beds at his disposal.

Like Paufique, Sourdille is a first-rate operator whom it was a delight and inspiration to watch. Although he does most of the preparation of his patients himself he gets through long operating lists surprisingly quickly and without apparent hurry. In one session fourteen, mostly major, operations occupied three hours and a half.

Theatre Technique.

Asepsis is scrupulous. The surgeon and his assistants wear rubber gloves—Sourdille always wears English ones. Lighting is by a comparatively dim head-lamp combined with an almost dark theatre and dark towels. This is by design because he considers that a bright light may dazzle and startle the patient, especially during cataract and graft operations. The patient is operated on on the trolley which brings him to the theatre, the surgeon and his assistants being seated.

Keratoplasty.

We watched Sourdille do six grafts; two each of total lamellar, partial lamellar and partial penetrating. The main points in his technique are:

Penetrating.—(1) The pupil is dilated if the graft is to be 5 mm. or less in diameter, but it is contracted for larger grafts, in order to avoid the danger of the pupil border lying opposite the edge of the graft with increased risk of an anterior synechia.

(2) The eye is anæsthetized with cocaine and adrenaline drops and a retrobulbar injection of scurocaine and alcohol (5 to 1) is also given. The object of the alcohol is to minimize post-operative reaction and thus the tendency to a rise in intra-ocular pressure which is the most common serious complication of keratoplasty.

(3) Complete akinesia is achieved by injecting all four recti and the orbicularis with scurocaine and alcohol and some surocaine is injected into the lid margins.

(4) The size of the graft varies from 4 to 7 mm. The most common is 5 mm., though Sourdille says that there may be advantages in making it larger than this. He uses, as a rule, the same trephine for recipient and donor though he admits that this point is arguable and that a slightly smaller graft may adapt itself better to its bed in the cornea. (In my short experience I certainly prefer quite a loose fit of the graft in its bed.)

(5) The graft is cut first, i.e. before touching the recipient's eye. The donor eye which has been preserved since its removal—almost always from a cadaver—in liquid paraffin at 4° C. is washed in saline and held in a piece of gauze in the operator's left hand while the graft is being taken.

Great care is taken to ensure that the trephine is held absolutely vertical to the cornea and for this reason Sourdille advocates that the graft should always be taken from the centre of the cornea. In this context he does not approve of Amsler's method of cutting a graft from behind forwards on the isolated cornea since he feels that it is important to cut both donor and recipient corneæ in the same direction to ensure an accurate fit.

The trephine is carried right through the cornea into the lens to ensure that the graft is completely freed. The graft is then carefully washed and care is taken to ensure that it is free of any pieces of iris or lens. It is then placed in the folds of a dry piece of gauze on which is placed a fairly heavy instrument to prevent its being knocked on to the floor by a hasty movement on the part of the surgeon.

(6) The surgeon now turns his attention to the recipient. Sutures are put into each lid for retraction and held by an assistant. Sutures are also placed in the tendons of the internal and external recti and are held by a second assistant.

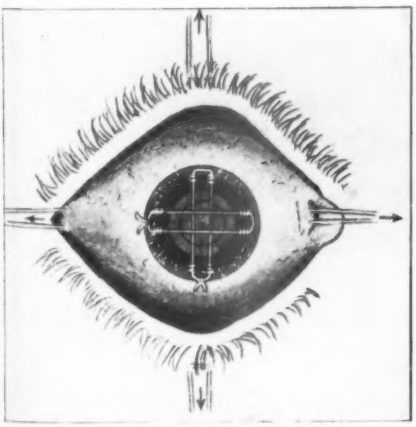


FIG. 1.—Sourdille's crossed sutures.

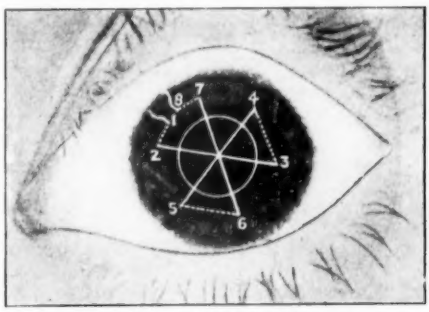


FIG. 2.—Katzin suture.

(7) The disc to be removed is marked with the trephine. Though Sourdille has a special ring for facilitating the accurate centering of the graft on the cornea we never saw him use it. After marking the cornea with half a turn of the trephine he lays the sutures which are to hold the graft in place. His method of suturing varies in different cases and I was not always quite sure why he chose a particular method. He most commonly uses double crossed sutures the bite at each end being purely corneal (Fig. 1).

He used a Katzin suture on one of the penetrating and on one of the partial lamellar grafts (Fig. 2). In the former he also put in two edge-to-edge sutures; this was because vitreous was present in the anterior chamber and he says that one should always employ two or more edge-to-edge sutures in these circumstances. He also sometimes puts a disc of thin rubber beneath the crossed sutures; he does this when there is a tendency for the graft to bulge.

(8) Having laid his sutures he trephines the cornea until the anterior chamber is opened; he then completes the removal of the disc, if necessary, with a rather large pair of double-curved scissors. He prefers this to any other method; there were certainly no tags of Descemet's membrane when he had finished (Fig. 3).

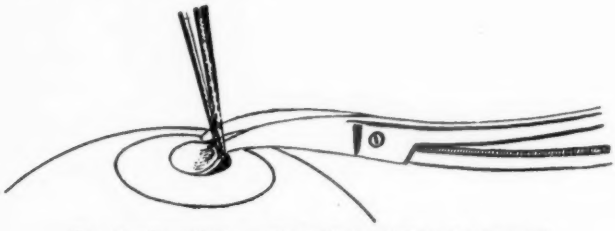


FIG. 3.—Sourdille's method of completing the removal of the disc from the recipient's cornea (penetrating graft).

(9) The graft is then put into its bed and fixed as I have already indicated. Atropine is instilled if the graft is not more than 5 mm. in diameter; if larger no drops are put in, or pilocarpine may be used.

(10) The patient's lids are sutured together and he is double padded.

Lamellar.

(1) The recipient's disc is removed first for two reasons; firstly to give time for any bleeding in the bed of the graft to stop and secondly because if, during the operation, it is found that the opacity is deeper than was at first thought it may be decided to do a penetrating graft instead of a lamellar.

(2) After one or two turns of the trephine the depth of penetration is investigated with an iris repositor. If it is not deep enough it is further deepened with the trephine—not, as in Paufique's technique with the tip of a Graefe knife.

(3) Having got to the required depth the edge of the disc is grasped with a pair of forceps and stripped off with Desmarre's "scarificateur" (Fig. 4).

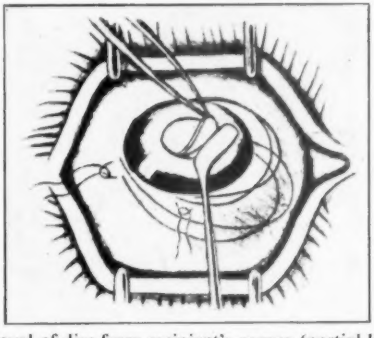


FIG. 4.—Removal of disc from recipient's cornea (partial lamellar graft).

The graft is cut as Sourdille describes in the symposium on keratoplasty which he wrote with Paufique and Offret (Fig. 5).

The graft is fixed in position in the same way as a penetrating graft.

(4) For a total lamellar keratoplasty both the recipient's disc and the graft are lifted in the same way, i.e. a suture is placed in the edge and is used to lift the graft as it is stripped off with the scarificateur in one piece—not, in the case of the recipient's disc, as is described in the book below mentioned (Figs. 6 and 7).

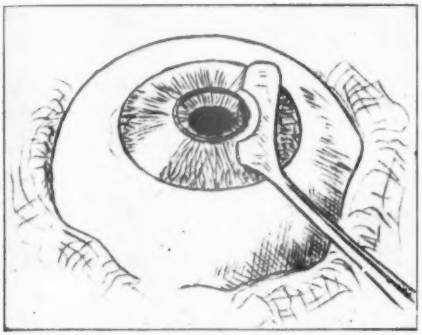


FIG. 5.—Sourdille's method of cutting lamellar graft (partial lamellar).

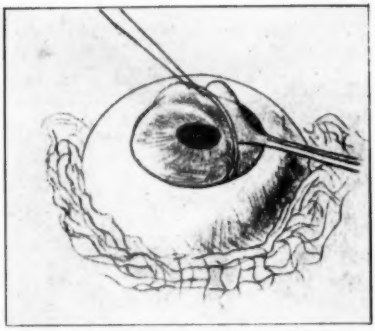


FIG. 6.—Sourdille's method of cutting recipient's disc and graft (total lamellar).

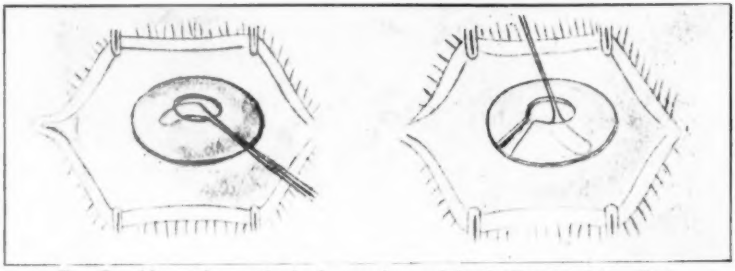


FIG. 7.—Alternative method of removing recipient's disc (total lamellar).

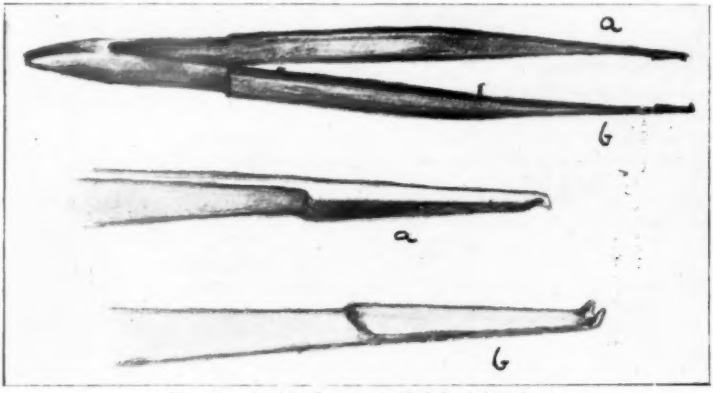


FIG. 8.—Jayle's forceps. (Original drawing).

Great care is taken to stop all bleeding points before laying the graft in position where it is fixed by edge-to-edge sutures.

Jayle's forceps are used by Sourdille as a general purpose instrument—for the conjunctiva, for sutures, for holding the recipient's disc in a corneal graft and so on. They have a "platform" on each blade behind the "one in two" teeth. They are stronger than straight iris forceps but are more delicate than conjunctival forceps (Fig. 8).

Accidental perforation of Descemet's membrane during the removal of the recipient's disc, which happened more than once, made no difference and the operation proceeded. As far as I know Sourdille does not, as a rule, do an intentional paracentesis before placing the graft, as Paufique does.

Notes On Cases

Altogether we saw Sourdille do 10 keratoplasties, 6 *in vivo* and 4 in cinematograph films.

(*a*) *Partial Penetrating.*

(1) For a central scar of unknown origin. A lamellar graft was intended but Descemet's membrane was found to be opaque so it was removed with the trephine and scissors and a penetrating graft put in.

(2) Leukoma adhaerens with vitreous in the anterior chamber. The recipient's disc was removed as usual, the synechia being separated from its under surface. The graft was fixed with a Katzin and two edge-to-edge sutures.

(3) A quiet disciform keratitis.

(*b*) *Partial Lamellar.*

(1) A peripheral graft in a case of severe active I.K.—purely as a therapeutic measure (4 mm.).

(2) A superficial central scar (6 mm.).

(*c*) *Total Lamellar.*

(1) An absolutely hopeless-looking staphylomatous opaque cornea due to I.K.

(2) An equally hopeless-looking scarred cornea following burns.

(3) A case of scarring due to burns in which the total lamellar was a preparatory graft to be followed later by a penetrating one.

(4) A case of band-shaped keratitis due to Still's disease.

We thus saw all three indications for lamellar keratoplasty applied: optical, therapeutic and preparatory.

Discussion

In a short discussion on keratoplasty which we had with Sourdille I gathered the following points:

(1) He gave the impression that keratoplasty is applicable to almost any corneal disease.

(2) Grafts are either optical, therapeutic or preparatory.

(3) *Penetrating* grafts are always optical and should never be used for therapy; also, they should only be employed on quiet eyes, when there is a fair amount of normal corneal tissue present and when there is not excessive vascularization, especially if it is superficial.

(4) *Lamellar grafts* may be optical, therapeutic, or preparatory, and they may be employed successfully in the presence of active inflammation, e.g. disciform keratitis and immediately after burns.

It is suggested that a total lamellar graft should be employed in the first few days after bad chemical burns. This is rational, but I understand that Paufique has not found it so successful as Sourdille. Lamellar grafts are also used therapeutically in cases of chronic and recurrent simple herpetic keratitis and in serpiginous ulcers—it will be remembered that Black reported a remarkable instance of the latter at the last meeting of the O.S.U.K. though he used a penetrating graft.

As preparatory grafts they may be used in badly scarred or vascularized corneæ, and in band-shaped keratitis in preparation for penetrating keratoplasty—such grafts are usually total.

A lamellar graft is also suggested for Fuchs' dystrophy and for rosacea keratitis but opinions differ on their success in such cases.

It is noteworthy that glaucoma has not been found to be the menace in lamellar keratoplasty which it is in penetrating. It used to be routine to trephine the eye at the end of the lamellar operation but this has now been discontinued.

Finally it is worth while mentioning a point which struck me, namely the absence of special devices such as punches, nibblers for tags of Descemet and such like. Simplicity was the hall-mark of the surgery we saw.

For the reproduction of Figs. 1–7 I gratefully acknowledge permission granted by the authors and publishers of "Les Greffes de la Cornée," a report presented to the Société Française d'Ophtalmologie by Paufique, Sourdille and Offret and published by Masson et Cie, Paris, in 1948.

Mr. H. E. Hobbs said that he had spoken to Dr. Paufique in Lyons on the subject of the prophylaxis of post-operative hypertension and he had been told that this complication was now much less feared in Lyons than formerly. Trephine operations were no longer employed as a routine measure, but he had seen Dr. Paufique perform a paracentesis with the keratoplasty on several occasions.

Mr. A. McKie Reid asked whether in these cases the Wassermann test had been carried out on the donor.

Mr. Lister said that he did not think it mattered. He could not believe that the spirochæte would survive for forty-eight hours under the conditions in which the donor eye was preserved.

Dr. E. C. B. Ibotson asked what percentage of cases became opaque after this operation.

Mr. Lister replied that the prognosis varied according to the condition for which the operation was done. In some cases, such as familial dystrophies, there was 100% chance of success; in interstitial keratitis about 50% chance, and in severe burns the chances were very much less.

Mr. Foster said that they had found it difficult to get a clear-cut answer to this question of success percentages, but of perforating grafts about 45% appear to show varying degrees of visual improvement.

Lamellar grafts are performed in many cases for therapeutic or tectonic reasons, where no immediate visual improvement is expected, with a very high percentage of structural success. When employed to improve vision they are applied to a wider selection of cases than the perforating type and the percentage of visual successes would appear to be lower.

Mr. B. W. Rycroft said that there was one precaution to bear in mind with a lamellar graft. It was difficult beforehand to assess the depth to which a scar penetrated in the cornea. One worked on a diffuse nebula, and very often started off with the idea of doing a lamellar graft and had to abandon that procedure, before finishing, for a total graft.

Mr. Foster said that it was, on occasion, very difficult to judge the depth of the lesion but when this was pointed out to the French surgeons they replied: "If the lesion is deeper than anticipated you can either convert the operation into a penetrating graft or perform a penetrating graft later."

[*December* 8, 1949]

RETROLENTAL FIBROPLASIA

Mr. P. McG. Moffatt: *Clinical Aspects of Retrolental Fibroplasia.*

No paper has so far appeared in this country under the title of Retrolental Fibroplasia. I can find only one report of a case, which Galloway showed at a clinical meeting of this Section in February 1948 at Birmingham (*Proc. R. Soc. Med.*, **41**, 724). Practically all the references are to be found in the American journals in which there is a very considerable volume of literature following the original report of Terry (1942a). This was a preliminary report under the heading "Extreme prematurity and fibroblastic overgrowth of persistent vascular sheath behind each crystalline lens".

Five other cases were cited, in which the findings were similar. All were premature, weighed 3 lb. or less at birth and had no evidence of hereditary factors.

To this clinical description, which had not previously been reported, can be added photophobia, shallow anterior chambers, opacities in the cornea and fine vessels visible on the retrolental membranes, persistence of the blue-grey colour of the iris which he called the "Fœtal blue colour", and failure to develop normal iris pattern. As the disease progresses the shallowness of the anterior chamber increases, posterior synechiæ form, and the affected eyes do not grow normally, becoming microphthalmic and the corneal diameter less than normal (this last is a point in differential diagnosis from retinoblastoma in which the cornea is unlikely to be smaller than normal). Glaucoma usually without hydrophthalmos, and cataract frequently develop. Anterior synechiæ form, the opacities in the cornea increase and the globe shrinks. The dentate processes mentioned in the original account were subsequently recognized by Terry as ciliary processes, narrowed and elongated, sometimes lacking pigment at their tips. Retinal detachment is a frequent complication.

To this condition, believing it to be due to a fibroplastic overgrowth of embryonic remains in the interstices of the vascular network of the posterior tunica vasculosa lentis, Terry (1942b) gave the name "Retrolental Fibroplasia", on morphological grounds so that it should be free from causal suggestions. In course of time he came to regard a great many developmental abnormalities as part of the disease and believed they arose from persistence of the hyaloid system, the presence of embryonic connective tissue behind the lens, or persistence of the fœtal character of the vitreous. The degree of fibroplasia could vary very widely in extent. The condition is rarely found in full-time infants and is usually unilateral when it occurs.

Terry was the first to observe the condition develop after birth in three cases, the postlental membrane began to form at the extreme periphery of the lens and covered the whole of the posterior surface within two weeks.

Owens and Owens (1949a) and Gilger (1949) found an incidence of about 7% in premature infants weighing 4½ lb. or less at birth. From Boston (Terry, 1945a; Clifford and Weller, 1948) figures are quoted as high as 23% for infants under 3 lb. The incidence appears to vary in different places, and even in different nurseries in the same city (Terry, 1945b). There is some evidence that the disease increases inversely with the birth-weight. Whereas the bilateral cases have increased, there is, according to Reese, no increase in incidence in the unilateral cases.

The prognosis in the fully established condition is bad. The eyes become blind and shrunken in many cases, but Terry found that in a small number where the eye grew normally the membrane behind the lens retrogressed and gaps appeared in it. The vision, however, remained very poor on account of associated changes in the retina.

Angiomatous lesions of the skin were reported in 15% of one series of cases (Reese and Payne, 1946a), and in 20% of a series of 100 cases by Terry in 1948. Mental retardation was not found to be more prevalent than in any series of premature infants, but Krause considered that most cases, if examined after the age of 4 years, would be found to be mentally retarded. He believes that the disease is due to aplasia of the anterior neural ectoderm and that retrolental fibroplasia is only a part of a wider failure to develop the anterior portion of the central nervous system.

Owens and Owens observed a large series of premature babies from birth and state that the first changes are dilatations on the retinal blood-vessels followed by swellings in the periphery of the retina and massive exudates going on to detachment. In their opinion the post-lental membrane is formed by the fusion and organization of the retinal folds behind the lens, and the vessels seen in the membrane are derived from the retinal vessels and not from a persistent hyaloid system as was thought by Terry. Out of the series 9 cases of this condition were found and observed. None had any evidence of persistent hyaloid or tunica vasculosa at birth, the eyes appeared to be normal. The disease manifested itself between the 2nd and 4th month of post-natal life.

Gilger (1949) examined a series of 229 cases of premature infants and found a similar incidence, no case occurring in an infant weighing more than 4 lb. at birth. There was no statistical evidence to show that race, age, parity, ante-natal bleeding, virus infection, or chronic illness, tuberculosis or syphilis in the mother, had any influence on the ætiology. Nor did she find that the cause of onset of premature labour, or the post-natal management of the infants were factors in the ætiology. Males were more frequently affected than females, and it has been suggested that the disease might be sex-linked as in one series of 150 cases, 95 were males (Bakwin, 1946). Gilger could form no conclusions from her series as to the role played by vitamin A. Warkany and Schraffenberger (1946) showed that rats developed a similar condition if the mothers were on a low vitamin-A diet. Jackson and Kinsey (1946) repeated this work with the same results but doubted whether the vitamin-A levels fall as low as those in experimental animals.

Gilger did not find that the increased incidence of the disease was related to increased survival rate of premature infants. Reese and Payne (1946b) consider that the lesion is due to persistence of the primary vitreous, with or without hyperplasia and that it is present at birth. Reese criticizes the concept of Krause on the grounds that the eye signs are not a dysplasia of the retina but fibrous tissue in the vitreous, and maintains that remains of the hyaloid artery are present which would not be expected in a dysplasia. He also disagrees with Krause's interpretation of his finding of mental retardation in his cases examined after the age of 4 years, and states that if cases of hydrocephalus are excluded, only 30% show mental retardation, a figure which might reasonably be expected in any series of premature infants. He also criticizes the work of Owens and Owens who state that there are no persistent embryonic structures at the onset, on the ground that these lie at the very periphery of the fundus and may have been missed unless the infant were examined with pupils fully dilated and under general anæsthesia. Reese recognizes two clinical entities: (1) Persistence of the primary vitreous with hyperplasia occurring in full-term infants of normal development and usually affecting one eye only. (2) True retrolental fibroplasia in which only a portion of the primary vitreous remains in the region of its base, and is bilateral.

Exposure to light was early considered as a possible factor in the ætiology but it has been shown by Hepner and others (1949) that the disease develops even when the eyes are covered until a weight of 4½ lb. has been attained.

It is rare for more than one case to occur in a family except in twins either identical or fraternal. Terry (1948) considered twinning a factor only in so far as it is a common cause of prematurity. Others have suggested that the disease is due to a low-grade infection of the uveal tract. It will be seen that opinions differ widely as to the cause of the condition, when it starts, or from what tissues the membrane is derived.

The differential diagnosis is from retinoblastoma, cataract, and intra-ocular infection leading to cyclitic membrane and pseudo-glioma.

Treatment by operative measures is most unsatisfactory. The lines of attack have been: (1) Needling the lens and cutting a trap-door through the opaque membrane. (2) Dragging out the opaque tissue by the posterior route and cutting it off. Terry considered this was dangerous as portions of ciliary body would almost certainly be pulled out along with the membrane. On the other hand Reese has operated on 11 cases and claims improvement in 3. He says that this method is only suitable in his first type of case. I have tried needling in two cases and found the operation difficult because of the shallowness of the A.C., and the lens does not absorb readily. One case I needled five times and still the greater part of the lens remained after six months. This child is now in a Sunshine Home and I have recently had the opportunity of examining the eyes about a year after the last operation. The pupil is filled by the calcified remains of the lens to which the iris is adherent. There is doubtful perception of light but this also applies to the other eye which was not needled. Both eyes are microphthalmic.

It has been suggested that some cases in which needling of cataracts in infants has failed might also have retrolental fibroplasia.

In view of the difficulty of achieving any useful result by operative measures, Terry suggested that it might be wiser to wait upon events as some cases improve spontaneously. Radiotherapy with a view to closing the blood vessels in the membrane and also to inhibit the growth of the fibrous tissue, has been found to be valueless.

Owens and Owens (1949b) applying the facts learned from experiments with chicks, viz. that high doses of vitamin A and iron inhibit the availability of vitamin E leading to encephalomalacia, studied three groups of premature infants. The first group were treated in the usual way with high protein diet, high vitamin A and iron intake. The incidence of retrolental fibroplasia was the usual figure of 12 to 25%. The second group were given a new water-miscible vitamin E preparation and less vitamin A and less iron than the first group. No instance of development of the condition was seen. The third group in whom the disease was just becoming apparent were treated with addition of the vitamin E preparation and reduction in vitamin A and iron intake, and retrogression or cure of the disease resulted. If this work is substantiated it will mark one of the major advances in the prevention of blindness.

I have had under my care 6 cases, 2 (twin brothers) have been available at this meeting and I have drawings of the eyes of another. The remaining 3 are in Sunshine Homes.

In order to obtain some idea of the incidence of the disease here I have inspected the records of all children in the six Sunshine Homes in this country, and, by kind permission of the National Institute for the Blind, have examined personally every case in which the diagnosis of retrolental fibroplasia had been made or could be suspected.

Out of 119 children being cared for in the 6 Sunshine Homes at the time of the investigation there were 12 cases in which the diagnosis of retrolental fibroplasia could be made with reasonable certainty, two others were doubtful. The first, male, aged 2 years was nine weeks premature and weighed 2 lb. at birth, the right eye had been enucleated and reported on pathologically as pseudo-glioma, the left had posterior synechiæ and an opaque membrane behind the lens, no other information could be obtained. The second child, female, aged 2 years 5 months, ten weeks premature, weighing 2 lb. at birth, developed opaque membrane behind both lenses and posterior synechiæ during the 3rd month whilst suffering from a virus infection of the gastro-intestinal tract. It was felt that this case was due to an infection although Gilger includes a similar case in her series.

Of the 12 cases, 7 were girls and 5 were boys, prematurity varied between twelve and eight weeks, average was nine weeks. Birth-weight varied between 3 lb. 8 oz. and 2 lb. 6 oz. Only 4 were less than 3 lb. There were 2 sets of twins—4 cases, one survivor of twins, and one the sole survivor of triplets.

The age at which the disease was first noticed was recorded as 2 months in two cases, 3, 5, 10 months respectively in three cases and "uncertain" or "probably from birth" in the remainder.

The youngest child at the time of examination was 1 year 8 months and the oldest 5 years. The average age was 2 years 9 months. Three were regarded as mentally retarded by their teachers, but severely retarded cases are not accepted by the Homes. In no case was there any history of blindness in the parents. In one case there was maternal bleeding three months before birth, and the mother of one case had taken large doses of quinine at the 2nd month of gestation. Otherwise the pregnancies had been recorded as normal. No details of the post-natal management were available. All the cases were in an advanced stage of the disease and the early signs had been obscured by secondary changes. Three cases

had severe corneal scarring, 1 case was buphthalmic in one eye, the remainder were microphthalmic in varying degrees. Posterior synechiæ were frequently found as also remains of anterior pupillary membrane. Definitely raised intra-ocular tension was found in one child in both eyes which were microphthalmic. In every case where it was possible to see through the pupils a greyish membrane or mass could be seen immediately behind the lens, though it did not obscure the fundus reflex completely in all cases. Five cases are awaiting admission to the Homes, of these 3 are boys and 2 are girls. One of the boys, in whom the defect was noticed at 6 months, weighed 4 lb. 3 oz. at birth and has a twin sister unaffected.

The diagnosis of retrolental fibroplasia is being made more frequently in this country but the numbers do not as yet approach anything like the incidence reported in America, where it is regarded as one of the major causes of blindness in infants.

I would like to take this opportunity of pleading for some machinery to be set up for the systematic examination of the eyes of all prematurely born babies during the first 6 months. It would also be helpful if more detailed notes were made concerning family history, the pregnancy, the post-natal management, the ocular history as well as the clinical findings when these cases are brought to hospital.

My thanks are due to the National Institute for the Blind for permission to visit the Sunshine Homes and examine the cases and records, to Dr. C. T. Potter and to Dr. J. K. Martin for details of the cases shown here:—

D. R. and A. R., male twins, born 17.1.49. Pregnancy normal. First children of young parents. No family history of blindness. Born 8 weeks prematurely. Birth-weights:—D. R. 2 lb. 12 oz., A. R. 2 lb. 8 oz. There was one placenta and chorion.

D. R. developed conjunctivitis at 2 weeks, and had a course of penicillin drops.

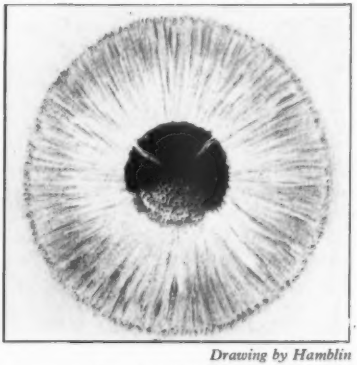
Both became rather anæmic. D. R. Hb 66%. A. R. 52%. Treated with iron. Discharged from hospital at 8 weeks weighing—D. R. 5 lb. 7 oz., A. R. 5 lb.

A. R. was admitted to the Evelina Hospital on 20.7.49, at 6 months old, for strangulated hernia. The parents had not noticed anything wrong with the children up to that time. Whilst in hospital it was noticed that A. R. had a roving nystagmus, microphthalmos, and a grey reflex in the pupils. The twin brother was then got up for examination and found to have a similar condition of the eyes.

Neither child attempted to follow a light or take hold of objects. They seem to be aware of a bright light, and a very faint reaction of the pupils can be obtained.

The irides have retained their fœtal blue colour, with lack of iris pattern. Well marked remains of persistent pupillary membrane are present in all four eyes. A grey membrane, in which one or two fine vessels can be made out, can be seen behind the lens in each eye.

The drawing shows the anterior pupillary membrane, the lack of differentiation of iris pattern and the grey reflex from the pupil (Fig. 1).



Drawing by Hamblin

FIG. 1.—Case D. R.

(Cases D. R. and A. R. were shown at the Section of Pædiatrics on *October* 28, 1949, *see* p. 235.)

A. F. C., 3 years old. Birth-weight 5 lb. 12 oz. Born one week prematurely, normal delivery.

This child was brought up to hospital when 11 months old. Examination under general anæsthesia showed whitish membrane behind the lower half of the lens and a grey mass in the vitreous behind it in each eye. The diagnosis was "Bilateral remains of the posterior vascular sheath of the lens".

He has been observed at intervals and appears to have enough vision to be able to avoid knocking into large objects.

The drawings were made very recently and illustrate the present condition so far as this can be reproduced in drawing (Figs. 2 and 3). The retrolental membranes are seen in the lower halves of the pupils, some fine vessels course over them. The atrophic retinæ are depicted as seen above the membranes. Very few retinal vessels could be made out and there were round or oval patches of degeneration. The lower parts of the retinæ were detached.



FIG. 2.



FIG. 3.

FIGS. 2 and 3.—Case A. F. C.

Both eyes are microphthalmic. The right eye has an ill-defined iris pattern and some strands of persistent pupillary membrane. The iris pattern in the left eye is better developed.

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Mr. Eugene Wolff (*From the Institute of Ophthalmology*): *Pathological Aspects of Retrolental Fibroplasia.*

Reese and Payne, Krause, Owens and Owens, and a number of others have each added some new facts to this disease entity. There are, however, a number of points that still seem obscure, the main ones being the nature of the retrolental vascular tissue, the cause of the retinal detachment which in a typical case accompanies the disease, and the curious usual time of onset—namely within the first six months after birth.

To understand retrolental fibroplasia from a pathological point of view it is essential I think to compare and contrast three conditions.

(1) Remains of the posterior vascular sheath or hyperplasia of the primary vitreous (Reese).
(2) The usual type of pseudo-glioma.
(3) Retrolental fibroplasia (Terry). Congenital encephalo-ophthalmic dysplasia (Krause).

(1) *Remains of the posterior vascular sheath or hyperplasia of the primary vitreous (Reese).*—This condition has of course been known a long time and there is a huge literature to which Treacher Collins and Parsons have made notable contributions.

Pathological anatomy: Here we find a saucer-shaped or pyramidal mass at the back of the lens. It is thickest in the centre and thins out towards the periphery where it may be absent, allowing a red reflex to be obtained in the living (Reese). The mass consists of connective tissue, cells and fibres and contains a varying number of vessels. Running forwards into the apex of the pyramid is (usually) the remains of the hyaloid artery. The posterior lens capsule may be intact or missing. In the latter case the fibrous tissue passes through the gap, the capsule at the edges being as a rule wavy and thickened. The lens itself is usually clear at first but may become opaque later. The retina here is not detached. The condition is present at birth and is most often unilateral. Pathologically therefore it is very different from the two other conditions.

(2) *The usual type of pseudo-glioma.*—This arises as a metastatic uveitis or retinitis and occurs as a rule in children of about 2 years. I would draw special attention to the fact that the signs of iridocyclitis in the anterior portion of the eye, that is the slight injection, the keratic precipitates and perhaps a synechia or two *come at the beginning of the ocular disease.*

Pathological anatomy: Here the anterior part of the eye up to the pars plana is usually almost normal; it is in the posterior portion that the main changes are seen. The retina is totally detached and it resembles a convolvulus flower. Posteriorly it usually forms a strand running forwards from the disc. I would emphasize that the detachment ends at the ora serrata. The retina is greatly thickened, a thickening which (again I would emphasize the point) goes right up to its site of attachment. It is also much altered. The funnel formed by the detached retina is filled by a vascularized connective tissue, and blood vessels can be seen to pass from the detached retina into the central strand. This central connective tissue reaches to the back of the lens and is continuous with the cyclitic membrane which is always present (Fig. 1).

The cyclitic membrane may be in any of the four stages usually described but as a rule consists of a vascularized connective tissue into which the clear and pigmented cells of the pars plana of the ciliary body have proliferated. This cyclitic membrane is attached to the retina and vessels pass out of the latter into the cyclitic membrane.

The cyclitic membrane is situated in the anterior angle between the detached retina and the pars plana. It is not well known that in the posterior angle between the detached retina and the pigment epithelium a vascularized pigmented mass often grows backwards from the junction of the ciliary body and the choroid at the ora serrata. It may be adherent to the outer aspect of the retina or to the pigment epithelium or to both. It goes through all the stages of the cyclitic membrane in front of the retina and indeed may be called a *retro-retinal cyclitic membrane* (Fig. 1).

The subretinal space is filled with a coagulated mass staining red with eosin and speckled with cholesterin crystals, which may be quite free from cells but usually contains desquamated degenerating pigment epithelial cells and fatty granular cells (ghost cells of Coats).

(3) *Retrolental fibroplasia (Terry). Congenital encephalo-ophthalmic dysplasia (Krause).*—It is of great importance to note that Owens and Owens by examining premature babies from birth found that a retinal detachment starting at the periphery preceded the retrolental membrane and the posterior synechiæ. They also established that all visible remains of the hyaloid system disappeared early in post-natal life.

Pathological Anatomy: Superficially a section of a typical case of retrolental fibroplasia resembles that of a pseudo-glioma. There is a complete detachment of the retina with a stalk posteriorly and a folded thickened retina anteriorly; there is the subretinal fluid staining pink with eosin and there is or *may be* a vascularized membrane behind the lens. But on closer inspection important differences are seen.

It seemed to me that the first problem to solve was to try and establish the nature of the retrolental membrane. Terry thought it had to do with the hyaloid system of vessels or the primary vitreous. But grave doubt was thrown on this hypothesis when Owens and Owens found that all visible remains of the hyaloid system disappeared early in post-natal life. In many of Krause's cases also there was no membrane at all.

Actually the membrane consists of vessels, which are usually capillaries, and connective tissue fibres which are exceedingly fine, the whole looking like embryonic tissue. But there can be little doubt that it is a cyclitic membrane! In the first place a cyclitic membrane is

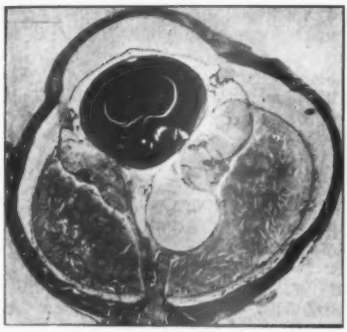


FIG. 1.—Pseudo-glioma. Retina completely detached and thickened right up to attachment at ora.



FIG. 2.—Retrolental fibroplasia (×26). (Mr. Gimblett's case.)



FIG. 3.—Retrolental fibroplasia. × 93. Note that detached retina is attached to pars plana by ciliary epithelium.

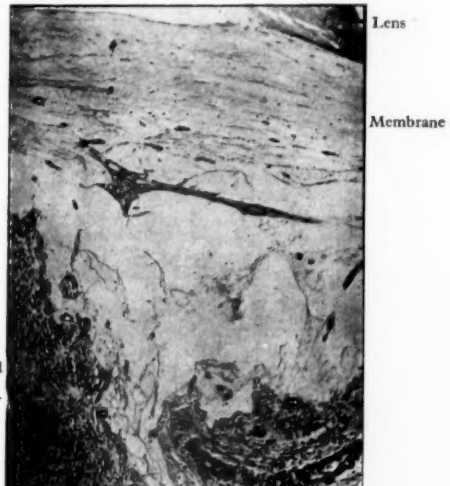


FIG. 4.—Retrolental fibroplasia. × 43. Note retrolental membrane consists of connective tissue, vessels and proliferated clear cells of ciliary body.

by far the commonest cause of a pathological vascularized tissue behind the lens and very good reason must be produced in any given case to prove that it is not (Figs. 2 and 4). Here the membrane consists not only of vessels and fibres but of proliferated epithelium which can quite easily be traced to the ciliary body. Also the membrane as observed clinically appears to develop from the periphery. Only, I would suggest that in retrolental fibroplasia the cyclitic membrane is produced by a very much milder toxin than that in a pseudo-glioma above described.

This is further shown by the fact that I have found only the clear cells of the pars plana growing into the membrane and not the pigmented ones as well. A retro-retinal cyclitic membrane has not been seen. Now a cyclitic membrane signifies inflammation. Actually the signs of inflammation are exceedingly slight but that inflammation does supervene is shown also by the posterior synechiæ which often appear during the course of the disease.

Having established this fact the next was to look for a cause for this mild iridocyclitis. A probable cause was to hand in the presence of the retinal detachment; for we have all had cases of retinal detachment returning after months or years with a ring synechia. Fuchs showed that the reason for this was that the subretinal fluid became toxic and if injected into the eye of an animal could produce an iridocyclitis. *This type of iridocyclitis usually supervenes months or even years after the detachment;* but it is also important to mention that it may never occur.

The next step was to look for the cause of the retinal detachment. This I think is in a typical case to be found in the remarkable difference between the appearance of the detachments in pseudo-glioma and retrolental fibroplasia *in their anterior portions.* In pseudo-glioma the retina, as mentioned before, is thickened right up to its attachment at the ora serrata; in retrolental fibroplasia it usually terminates in a thin portion which looks like the clear cells of the pars plana and is attached at varying distances along the pars plana (Figs. 2 and 3). Krause tells us that in a number of his cases the detachment went right up to the first ciliary process. Now the clear and the pigmented cells of the pars plana unite at about the third month of intra-uterine life and this union is very firm. Hence retinal detachments normally end at the ora.

The meaning of the fact that the detachment continues on to the pars plana is most probably that there has never been proper union between the clear and pigmented cells. Later, one would suggest, a true detachment takes place by fluid collecting between the two layers and gradually spreading backwards.

The above is an account of a typical case. But the abnormality of the retina may be present in a great many other forms. Thus the detachment may be present in its posterior part only or there may be folds in it forming a septum and so on.

It would seem then that in a typical case the course of events is as follows:

A "noxious stimulus" reaches the embryo very early, probably in the first few months of intra-uterine life. Its effect on the eye is primarily on the retina which remains non-attached in part or as a whole. (The noxious stimulus may affect other parts of the organism especially the brain as pointed out by Krause, hence his name for the disease—Encephalo-ophthalmic dysplasia.) Fluid collects under the retina and a real detachment is produced which gradually becomes total. This may give rise to a mild uveitis which is responsible for the retrolental membrane and the posterior synechiæ *when these are present.*

My thanks are due to Mr. Peter Hansell, Dr. Norman Ashton, and also Mr. McNeil.

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Mr. C. L. Gimblett : *Retrolental Fibroplasia*

Child aged 1½ years.

This baby was first brought to see me on January 2, 1948, when he was 6 months old. His mother had had five previous miscarriages and this child had been 9 weeks premature and weighed 2½ lb. at birth. Before I saw him the child's mother reported that he did not recognize her. He had nystagmoid movements since birth and mother noticed at 4 months that his sight was defective. She felt, however, that he always had perception of light and that this has improved considerably.

Mr. E. Wolff, who saw the case with me, agreed that there might be present bilateral retinal gliomata and that it would not be safe to leave the child without investigation. So on January 6, 1948, the left eye was removed and Mr. Wolff has described the microscopic appearances.

Neither the child nor his mother showed any abnormality in red or white blood cell counts or colour indices. In both, Wassermann and Kahn tests were negative. The right eye—on dilating the pupil—shows a good red reflex except on the temporal side where it is obscured by a whitish opacity spreading forward from the ciliary region *behind* the lens.

On the nasal side there is a retinal detachment.

From the first the child has shown a complete absence of any pain and as time has gone on he has developed normally and is now walking well.

About April 1949 the iris adhesion which is now to be seen at 9 o'clock was first noticed.

I could not accept the responsibility of telling the mother that another pregnancy would be free from risk of a similar tragedy.

Mr. A. J. Cameron: *Ocular Defects in Premature Twins*

The female monovular twins shown were born prematurely at the 6½ month. One (J.) weighed 2 lb. 11 oz. and the other (M.) weighed 3 lb. Such difficulty was experienced in keeping them alive in oxygen tents that they were 4 months old before doubt was expressed as to their ability to see.

On examination at that time: M. had partially opaque corneæ; anterior synechiæ of the pupillary membrane; opaque lenses; no fundus reflex and marked nystagmus. J. had in the right eye the same condition. In the left the lens was clear with a persistent, posterior, vascular capsule. Nystagmus was present in this case also. In both M. and J. there was practically no anterior chamber.

There would appear to be a current belief that a true retrolental fibroplasia has a free pupil, but I feel sure that this is not a necessary feature. Terry (1946, *Journal of Pædiatrics*, **29**, 770) makes no mention of this point but stresses two points which are very definitely present in these cases, namely the prematurity of the children, and the absence of other abnormalities. One admissible exception to this would appear to be angiomas in the skin and, for what it is worth, each of those children has a nævus, one beside the ear and the other child has one on her wrist. A free pupil has not been mentioned as a necessary feature in the many cases of Terry's syndrome recorded in America.

I am not able to give any opinion as to the condition of the retinæ in either case so that whether or not any of the variations which have been described, such as dysplasia of the retina or hyperplasia of the primary vitreous, are present I cannot say. It can be seen that the children are in excellent health, and appear of normal intelligence. They are now about 3 years old. There is no history of the mother having had any particular illness during the period of gestation.

Many cases which previously have been labelled "pseudo-gliomas" may have been of this type. Since the original examination there is no doubt whatever that the degree of corneal opacity has very much increased and, to-day, so much so that the details behind the cornea can only with difficulty be seen. This is particularly marked in the child (M.) with both corneæ affected, but also holds for the other child (J.), to a lesser degree, in which originally only the one eye showed any marked corneal opacity.

Mr. Norman Fleming: *Retrolental Fibroplasia in Monovular Twins*

In this case of twins, almost certainly monovular, all four eyes were blind.

The mother, aged 37, was married in 1935 when she was 23 years of age. She had abortions in 1937 and twice in 1940, a premature child who died in 1941: in each case the blood pressure was raised. In 1944 a boy was born after medical induction on account of swollen ankles and high blood pressure: this child is alive and well.

In 1945, the twins were born at 33 weeks as the result of spontaneous premature labour and each weighed 3½ lb. The mother had not felt well from the beginning of pregnancy; she suffered from backache and albumin was found in the second month. She was kept in bed at home and subsequently remained in hospital for nine weeks following delivery, in order to breast feed both infants. They were brought to me and found to be blind when aged 3 months.

The mother gave no history of any infectious fever. Her eyes had not been examined during pregnancy but she had not experienced any loss of sight; the fundi were found to be normal and vision 6/5 right and left. Both parents had negative W.R. The mother is Rhesus negative and has a blood urea of 42. E.S.R. 11. R.B.C. 4 9 m.; Hb 87%.

On superficial examination of the twins, all four eyes gave the impression of a glioma of the retina but on closer examination it was found that the pupils were inactive, that it was impossible to find any normal fundus around the "growth" in any eye and that transillumination gave no definite sign of a tumour at any point.

I took the babies to see Mr. E. Wolff and we decided to remove one eye for diagnosis; I am indebted to him also for his examination of the eye after removal.

The eye is a very small one, measuring only 12 mm. from front to back and 11 mm. transversely. The retina is detached and very atrophic. The detachment does not reach to the ora serrata thus differing from the typical case described by Wolff at this meeting. Also there is no retrolental membrane; but the clear cells of the ciliary body are partly detached and are proliferating. The choroid is largely atrophic and there are numerous colloid bodies on Bruch's membrane. Posterior synechiæ are present.

Both twins were found to be suffering from a severe achromatic anæmia for which they were treated for some time, but, the eyes being quiet and no other pathological condition being found, they were sent to the Sunshine Home. They are there now, and are, I understand, in good health.

Dr. V. Mary Crosse

In the City of Birmingham there have been over 5,000 premature births (5½ lb. or less at birth) since January 1945. Of these 4,000 have been followed to the age of 1 year and only 4 cases of retrolental fibroplasia have been found. This gives a case incidence of 0·1 % of all premature babies, 0·8 % of babies under 4 lb. and 4·2 % of babies under 3 lb. Of the 4 cases 2 were binovular twins. The following particulars may be of interest:

Place in family: 1st pregnancy (1 baby)
3rd pregnancy (3 babies)
Maturity: 32 weeks (2 babies)
30 weeks (2 babies)
Ante-natal complications: None
Season born: May (3 babies)
August (1 baby)
Type of birth: Normal vertex (2 babies)
Breech (2 babies)
Birth asphyxia: Present (2 babies)
Absent (2 babies)
Air entry: Poor in all cases
Body temperature: Well maintained in all cases
Œdema: Present (2 babies)
Absent (2 babies)
Jaundice: Mild (3 babies)
Absent (1 baby)
Cyanotic attacks: Severe (3 babies)
Slight (1 baby)
Anæmia: Severe (1 baby) (Two transfusions given)
Absent (3 babies)
Wassermann: All negative
Rh factor: Mother positive (2 babies)
Mother and babies negative (2 cases)
Skin nævus: Present (1 baby)
Absent (3 babies)
Eye infections: None
Other infections: Pneumonia (2 babies)
Abscess of submaxillary gland (1 baby)
None (1 baby)

Various forms of treatment have been put forward from time to time as possible causes of retrolental fibroplasia. Particulars of such treatment are as follows:

Vitamin A: 15,000 i.u. given daily from age of 2 weeks in all cases (water-miscible form never given).
Vitamin E: (Only given in 2 cases after the condition had developed.)
Iron: Given from age of 6 weeks in 3 cases and from 8 weeks in the fourth.
Hormones: None given.
Parenteral blood or plasma: None given.
Exposure of eyes to light: Eyes shaded by thick rubber oxygen mask for five weeks in one case. Other cases treated in Queen Charlotte type of Oxygenaire in rooms with normal lighting.
Penicillin: Given to 3 out of 4 cases for various infections.
Oxygen: Administered for nineteen days, twenty-six days, four weeks, and five weeks respectively.
Feeding: High protein cows' milk, with exception of one case which was given breast milk for the first seventeen days of life.

In all 4 cases the condition was bilateral. In 2 of the babies the fundi were examined at the age of 2 months and appeared to be normal. The condition was discovered at 1 year (1st case), 4 months, 3½ months, and 3 months respectively. In all cases the child appears to be mentally normal. In 1 case a subconjunctival membrane graft was made by Mr. Jameson Evans. In 2 cases large doses of vitamin E were administered and the administration of vitamin A and iron was stopped. One of these babies subsequently developed glaucoma, necessitating the removal of the eye by Mr. Jameson Evans (hæmorrhage was found to be the cause). The second died of pneumonia at the age of 5½ months and the eyes were examined post mortem by Dr. Baar.

In order to facilitate early diagnosis the following policy has been adopted in the Birmingham Premature Baby Units:

The fundi are examined as soon after birth as practicable (in all cases this is done before the age of 4 weeks), and subsequent examinations are made every two weeks, the pupils being dilated for the examination.

Mr. Jameson Evans said that through the kindness of Dr. Mary Crosse he had been able to see 4 of these cases, and he had seen a fifth recently. The case which he would describe was one in which the right eye had a complete retrolental fibroplasia, the left eye an incomplete. It was of some importance and interest from the point of view of the possible development of the condition. It would be seen from his picture (Fig. 1) that there arose from the region of the pars plana a fine ring of tissue which extended immediately behind the lens.

There were no remains of the central hyaloid system. The disc was pale, but, he thought, of normal contour, and there was an enlarged vein passing down in the lower part of the retina. The network showed some finely pigmented cells chiefly in the nasal and lower quadrant. The iris showed no changes suggestive of iritis, but this case had been observed only for three months. The mother, a Pole in a displaced persons' camp, could give little information, and there was no record of the birth-weight, but the child was eight or nine weeks premature.



Drawing by Hamblin

FIG. 1. — Left eye, showing ingrowth of ring of new tissue behind lens: incomplete retrolental fibroplasia.

The clinical features about this case were the shallow anterior chambers, the practically fixed pupils, and the very characteristic appearance of a bowl-shaped grey mass behind the lens in the right eye.

Dr. H. S. Baar showed lantern slides illustrating the histological findings in one of the twins mentioned by Dr. Crosse. There was a detached retina which enclosed a small amount of fibrillary vitreous body. Between detached retina and its pigmented layer there was a highly albuminous exudate with a few shed-off pigmented cells and ghost cells. Only in a few places within the vitreous body were blood vessels present. These were of capillary calibre and not surrounded by connective tissue. Numerous elongated cells posterior to the ciliary body were interpreted as proliferated endothelial cells. Such cells and fibrils of the vitreous were attached to the retina and tags were formed apparently as the result of traction. The ciliary processes were slender and long, but their blood vessels well developed. The clear-cell layer was normal in many places, but proliferation was seen in some and detachment in occasional areas. There were no synechiæ, the iris showed no inflammatory changes and in its vessel layer numerous branched chromatophores were seen.

Mr. P. M. Moffatt, in replying on the discussion, said that if he had omitted to mention corneal opacities, this was in error, but he did know about them. With regard to children born with this condition being members of the same family, in 1939 a mother brought her son aged 2 months to him with what might have been this condition. The child was full term and had weighed 9 lb. at birth. The child subsequently became totally blind and mentally defective, and was at present, aged 10, in a home for mental defectives. Two years later the mother brought her next child—a boy—to have his eyes examined. The eyes appeared to be all right, but two weeks later she brought the child again, saying he was going the same way as the other boy, and that proved to be so. He eventually excised one eye to establish the diagnosis, and the opinion came back "Pseudo-glioma". Three years later the mother gave birth to a child who was perfectly normal, and 2 previous children had been normal. In the children in the Sunshine Homes he saw no case, except those of twins, in which there was a familial connexion.

He had quoted a statement that in America *a* major if not *the* major cause of blindness in infants was retrolental fibroplasia, and that statement he thought he could substantiate. He did not believe it was the same in this country, but he was not prepared to give figures at the moment because of the lack of a proper reporting system. For example, he had heard that evening of several cases to which he had not had access, and unless there was some system of reporting these cases he did not think they could arrive at a figure for the incidence of the condition. How was some co-ordinating machinery for this purpose to be set up? On listening to Dr. Mary Crosse he was agreeably surprised to find that somebody was already doing what he had suggested, and he could not help feeling that in Dr. Crosse's cases the examination of the fundi was probably quite well covered.

Repeated examination need not take place in the very earliest days after birth, but just before the time when it was known that the disease might appear, namely, at the second month, when the membrane might spread across the lens in a matter of a few weeks, then he thought examinations should be made, at any rate at intervals of one week, if that could be done without in any way jeopardizing the viability of the infant.

The President asked whether, once the disease had started, there was any possibility of vitamin E arresting it.

Mr. Moffatt said that there was such a prospect in the early stages. It had been reported that by using a water-miscible preparation of vitamin E and cutting down the intake of vitamin A and iron, the process was arrested and the membrane disappeared.

Dr. Mary Crosse said that that had been tried in 2 of her cases, with no effect.

Mr. Eugene Wolff said that it was obvious from what had been stated that evening that the name "retrolental fibroplasia" was a misnomer. There could be no doubt that they were dealing with a disease entity. He suggested that it be called "Terry's disease". Nobody could quarrel with that, because it was he who put the disease "on the map".

Section of Pædiatrics

President—W. W. PAYNE, M.B., M.R.C.P.

[*October* 28, 1949]

Retrolental Fibroplasia Occurring in Twins.—J. K. MARTIN, M.R.C.P.

D. R. and A. R., male twins, born 17.1.49.

First children of young parents, no consanguinity. No family history of blindness. Born in the 29th week of pregnancy. Birth-weights: (1) A. R., 2 lb. 8 oz.; (2) D. R., 2 lb. 12oz. There was only one placenta and chorion. Lusty at birth and progress favourable. D. R. developed conjunctivitis at 2 weeks and had a course of penicillin eye drops. Both became rather anæmic. Hb: 52% A. R., 66% D. R. Treated with iron. Discharged from hospital at 8 weeks, A. R. 5 lb. and D. R. 5 lb. 7 oz.

Mother perfectly well throughout pregnancy.

A. R. admitted to hospital on 20.7.49, for operation for strangulated right inguinal hernia. Parents had not noticed anything wrong with the children up to this time. It was noticed that both children had a roving nystagmus and microphthalmos. No attempt to follow a light or take objects. They were aware of a bright light and the pupils reacted sluggishly. The red retinal reflex was absent. Mr. P. McG. Moffatt reported "Retrolental fibroplasia. Deficient differentiation of anterior layers of the iris. Adhesions from anterior surface of the iris to the lens capsule".

Both children are otherwise healthy and developing normally.

Investigations.—(1) *W.R. and Kahn:* mother negative on 9.9.48.

(2) *Blood Groups:*

	Group	Genotype	MN	S.	P.	Lewis	Lutheran	Kell
Mr. R. ..	A_2	r r (cde/cde)	N	+	+	—	—	—
Mrs. R. ..	A_1	R_1R_1 (CDe/CDe)	M	+	+	—	—	—
A. R. ..	A_1	R_1R_2 (CDe/cDE)	MN	+	?+	—	—	+
D. R. ..	A_1	R_1R_2 (CDe/cDE)	MN	+	?+	—	—	?

(*See also* p. 226, Fig. 1.)

Retrolental Fibroplasia in a Premature Baby.—A. WHITE FRANKLIN, M.B., F.R.C.P.

S. B., a first-born female, was born 3.1.49, at the 28th week. The mother had had a normal pregnancy with routine vitamins irregularly taken, and was admitted to Paddington Hospital with a threatened abortion two weeks after a fall on the abdomen.

Delivery was spontaneous, the mother being given sodium amytal 3 grains and pethidine 150 mg. The baby weighed 3 lb., measured 14½ inches with a skull circumference of 11 inches.

At first feeding was difficult, but after a period of tube feeding during the first week, progress was steady on expressed breast milk, and later on Humanized Trufood. Vitamin B (3 mg.), vitamin C (5 mg.) and adexolin (from 2–20 minims) were given daily. Much of the first month was spent in an oxygen tent. The baby left hospital aged 56 days, weighing 5 lb. 8 oz.

The mother suspected blindness at this time and at three months attended Moorfields Hospital where Mr. A. G. Leigh diagnosed blindness due to retrolental fibroplasia. He reported: "Very shallow anterior chambers, both eyes showing well-marked posterior synechiæ with atrophic irides. Both lenses were clear and a dense white fibrous membrane was seen in the vitreous immediately behind the lens in each eye." The right lens was needled without benefit.

Progress was at first steady but slow, and at 9 months she weighed only 11 lb. 13 oz. She then began to refuse feeds, to vomit, and to lose weight. At the age of 38 weeks (28.9.49) she was admitted to Saint Bartholomew's Hospital for feeding regulation. She weighs 11 lb. and appears thin, small and blind. She cannot hold her head steady nor sit up. The eyes appear sunken and small. Skull circumference is

16½ inches. X-ray of the skull is normal and shows orbits of normal size. Beyond the eye condition, which is as described above, examination reveals only a small hæmangioma in the right pubic region and pallor of mucous membranes (R.B.C. 5,000,000 per c.mm.; Hb 6·6 gramme per 100 c.cm. (48%); C.I. 0·49). Blood Wassermann negative.

This is a case of bilateral retrolental fibroplasia in a premature small baby, complicated by general failure to thrive, anæmia, feeding difficulty and marked delay in behaviour development. No unusual drug or vitamin treatment was given to either the mother or the baby. The baby, like so many small premature babies, spent much of the first weeks of life in an oxygen tent.

Examples of this condition have been recorded in England during the last seventy years (Nettleship, 1873). The late Dr. Terry of Boston (1942) first drew the attention of pædiatricians to the association with prematurity. Although relatively common in Boston this is still a rare disease in and around London.

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? **Periarteritis Nodosa.**—P. M. M. PRITCHARD, M.B.

Girl aged 4 years 8 months. Well until May 1948, when she developed puffiness of the eyelids which lasted two months. She was anorexic and miserable.

In July 1948 she had acute tonsillitis, treated with sulphamezathine. In the next eight weeks, she had recurrent evening pyrexia up to 101° F., night sweats, and a loss in weight of 5 lb.

Nothing relevant in the past or family history. Had never had a sulphonamide before.

She was admitted to hospital on September 24, 1948. Age 3½ years. Weight 27 lb. Tonsils septic. Widespread rash consisting of small flat-topped polygonal papules, surmounted by a minute vesicle. It became more prominent in the two days following tonsillectomy on October 6, 1948; lasted about eight months, then faded gradually leaving small, puckered scars.

Skin biopsy on November 30, 1948, showed "a granulomatous lesion in the superficial corium. Localized fibrinoid degeneration of collagen, aggregation of mononuclear cells mainly lymphocytes, epithelioid cells and fibroblasts, as well as a few foreign body giant cells. Œdema of precapillary vessels".

January 1, 1949: Transient pain in legs and flanks.

In February 1949 the liver began to enlarge, until it was 3 cm. below the right costal margin. The spleen became palpable a month later.

March 26, 1949: Bilateral basal pneumonia, after which she had albuminuria for three weeks. Urinary deposit normal.

During April 1949 there was gradual cardiac enlargement, with bilateral pleural effusions and congestion of the lung fields, followed in May 1949 by congestive cardiac failure. The electrocardiogram on May 30, 1949, showed a P–R interval of 0·28 sec. The cardiac failure improved with digitalis.

Irregular fever up to 101·5° F. during June and July 1949.

She returned to hospital on August 28, 1949, after two months' convalescence and was found to have a blood pressure of 165/120. Cardiac enlargement and hepatosplenomegaly were still present. No nodules. Good peripheral pulses. Tachycardia 110 to 130.

The hypertension has continued, unaffected by sedation. Albuminuria has been present for the past two months, with a slight increase in the red cells, white cells and casts.

B.S.R. persistently raised (28–48 mm.) throughout the illness, which has been almost afebrile. Moderate orthochromic anæmia (8·8 to 10·6 grammes Hb/100 ml.). White blood count between 7,400 and 14,600 per c.mm., with a normal differential count, and no eosinophilia. Antistreptolysin titre less than 20 units/ml. on

May 19, 1949. Renal function and intravenous pyelogram normal. Occult blood negative. W.R. and Kahn negative. Mantoux 1 : 100 negative on three occasions. Liver function tests within normal limits.

Muscle biopsy on October 8, 1949, showed "numerous granulomatous lesions in relation to small arterioles, consisting of macrophages, lymphocytes and young fibroblasts. There is necrosis in the centre of some lesions, but no caseation. In a few nodules giant cells of the Langhans type are present. The arterioles near the nodules show prominent endothelial lining cells, but no evidence of necrosis in their walls, only slight mononuclear cell infiltration.

The smaller nodules are highly reminiscent of Aschoff bodies (Figs. 1 and 2).



FIG. 1. × 95

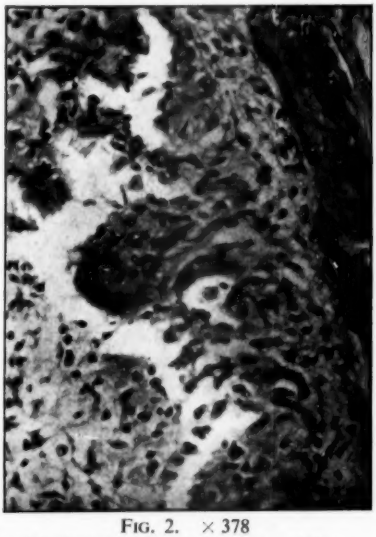


FIG. 2. × 378

Muscle Biopsy.—Showing granulomatous lesion with giant cells in relation to arteriole.

Comment.—Periarteritis nodosa, running a subacute course and affecting mainly the small arteries, would account for the rash, hepatosplenomegaly, myocarditis and hypertension.

As yet, no definite histological diagnosis can be made, though the lesions show some resemblance to the granulomata of periarteritis nodosa described in the lungs by Sweeney and Baggenstoss (1949); to the granulomatous arteriolitis of Teilum (1946), and to some of the heterogenous group described as non-specific focal myocarditis by Marcuse (1947). However, in the sections examined, no necrosis of the arterial wall has been seen.

It seems most probable that this case is one of the group of pathogenetically-related collagen-vascular diseases, with points in common with periarteritis nodosa and acute rheumatism, but, clinically and histologically, typical of neither.

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Persistent Left Cardinal Vein.—J. DEAN, M.R.C.P. (for I. M. ANDERSON, M.D.).

G. B., male, aged 7 years.

First seen September 1948.

History.—Breathless since birth but improving on the whole. Blue attacks recently.

On examination.—Slight build. Slight cyanosis. Left side of chest more prominent than right. Diffuse apex beat in fifth left space, ¼ in. outside midclavicular line. Loud first sound at apex. Apical second sound duplicated. Faint second sound at aortic area. Harsh systolic murmur at apex and in third and fourth left interspaces near sternum. Faint early diastolic murmur internal to apex. B.P. (arm) 95/65.

X-ray of chest: There is a persistent left cardinal vein with enlargement of the right ventricle.

Angiocardiogram: Interatrial septal defect with a right-to-left shunt and probably a number of abnormal arteries coming off the aorta.

E.C.G.: Right ventricular preponderance.

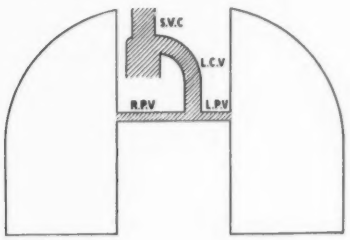


FIG. 1.—Probable arrangement of pulmonary venous system in case of persistent left cardinal vein. S.V.C. = superior vena cava. L.C.V. = left cardinal vein. R.P.V. and L.P.V. = pulmonary veins.

Multiple Cardiac Anomalies with Dextrocardia and Situs Inversus.—J. DEAN, M.R.C.P. (for I. M. ANDERSON, M.D.).

L. P., female, aged 20 months.

First seen July 1949 with blueness on exertion for ten months and severe cyanotic attacks.

On examination.—Thin, flabby child. Slight cyanosis at rest, marked cyanosis on exertion. Apex beat not definable. Heart sounds best heard in fourth left space near nipple. Harsh systolic murmur maximal at left border of sternum but audible all over heart.

X-ray of chest: "Cardiac apex is on right side. . . ."

X-ray of abdomen: Stomach is on right side.

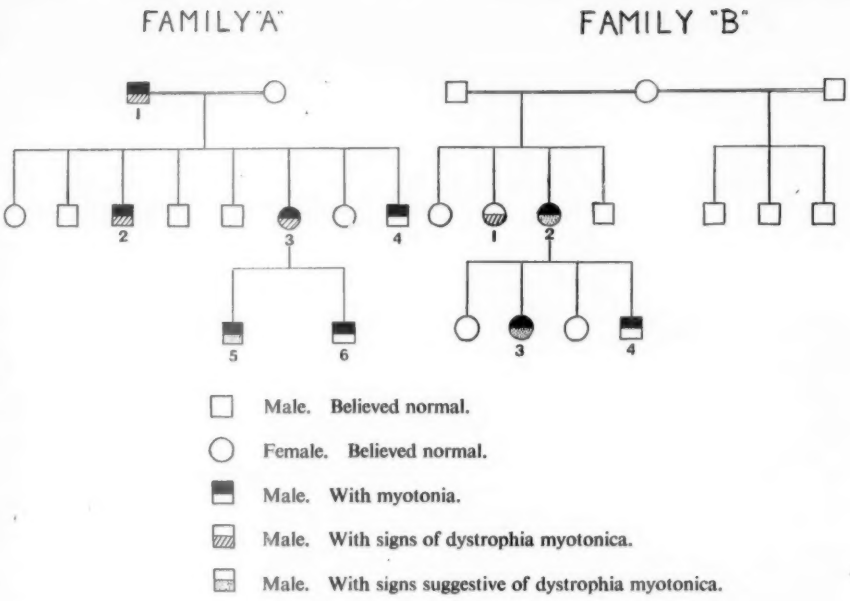
Angiocardiogram: "The superior vena cava lies on the right side. The contrast medium passes into both auricles simultaneously. The aorta fills as soon as the 'right' ventricle, but both ventricles fill almost simultaneously. The pulmonary artery arises from the 'left' ventricle which lies on the right side, but shows no evidence of stenosis" (Dr. J. H. Smitham).

Two Families with Myotonia.—D. A. J. WILLIAMSON, M.D., M.R.C.P. (for W. G. WYLLIE, M.D., F.R.C.P.).

FAMILY A

James T. (5) aged 10 years. Stiffness noticed since infancy, walking always difficult, particularly after sitting or standing still. Runs stiffly until he has become "loosened up". Hands and arms also stiff at times. The condition is worse when he is excited.

On examination.—Normal intelligence and appearance except for slightly excessive muscular development for age. No myopathic facies. Eyes normal. No cataracts seen. Genitalia normal. Slight but definite sluggishness in relaxing grip. Gait stiff at first but soon becomes normal. Tendon reflexes normal. Mechanical myotonia obtainable in most muscle groups, e.g. tongue, thenar eminences and calf. Minimal wasting of both thenar eminences with abnormal abduction of thumbs. E.C.G. normal.



Alan T. (6) aged 4 years. Stiffness of legs noticed at age of 2 years, which has become more marked. Symptoms resemble those of brother (*vide supra*).

On examination.—Normal facies. Normal build. Eyes normal. Gait stiff at first. Mechanical myotonia in usual muscle groups. No wasting. Tendon reflexes brisk. E.C.G. normal.

Family history.—Maternal grandfat er (1) had myotonia and cataract.

Maternal uncle (2), aged 49 years, has myotonia with slight muscle wasting.

Another maternal uncle (4), aged 37 years, has myotonia.

Both are living normal active lives.

Mother (3), aged 42 years, has had myotonia since childhood and now has slight wasting of thenar muscles with abnormal abduction of thumbs. Otherwise well (*see* Family Tree A).

FAMILY B

Jean D. (3) aged 16 years. Stiffness noticed at age of 1 year when it was observed that she would fall if placed on her feet but could stand if left to herself. Has always had difficulty with walking, particularly on gradients and stairs. Stiffness wears off after short period of exercise. Condition seems better in damp weather but is not affected by temperature. Worse if excited or harassed. She is now working without disability as a bookbinder.

On examination.—Rather thin-faced girl. Normal intelligence. Eyes normal. Slight wasting of thenar eminences. Definite sluggishness in relaxing muscles, e.g. grip or straightening knee. Mechanical myotonia obtainable in tongue, calf, thenar eminences, etc. E.C.G. normal.

William D. (4) aged 12 years. Symptoms not noticed until the age of 5 years : now closely resemble those of sister (*vide supra*) except that recently he has had attacks of severe cramp-like pain in the abdomen. These mostly occur at night and are relieved by warmth. Condition less severe in warm weather. He was treated with quinine hydrochloride 5 grains b.d. for several months with apparent improvement but treatment was suspended owing to toxic symptoms.

On examination.—Normal intelligence and appearance. Muscular development probably rather excessive. Eyes normal. No muscle wasting. Mechanical

myotonia obtainable at usual sites. Definite sluggishness in relaxing muscles. E.C.G. normal.

Family history.—Mother (2) has myopathic facies with receding hair and mechanical myotonia in tongue and calf. She has failing vision in the left eye, ? cause.

A maternal aunt (1) died aged 11 years suffering from mental deficiency and cataract.

Another maternal aunt has poor vision which has not been investigated (*see* Family Tree B).

Discussion

In both of these families the condition was undiagnosed for many years with the result that the unfortunate sufferers had usually been dubbed either lazy or naughty, especially since the myotonia is aggravated if the patients are harassed.

Nomenclature.—In the classical accounts of myotonia three separate conditions are described:

(*a*) Myotonia congenita or Thomsen's disease is a familial complaint often appearing in early childhood in which myotonia with muscular pseudo-hypertrophy is the only symptom.

(*b*) Dystrophia myotonica is also a familial complaint but it does not usually appear until adolescence, although cases as young as 2 and 3 years have been described. The myotonia is usually less marked and is uncommon in the lower limbs. It is accompanied by muscle wasting particularly of the facial, sterno-mastoid, forearm and thenar muscles. There are also a number of very important associated conditions. These include: Cataract; fronto-parietal baldness; cardiac changes (P-R interval prolonged); genital atrophy; mental and social deterioration.

(*c*) Paramyotonia is a condition in which myotonia occurs only in cold weather.

According to some authorities, notably Maas and Paterson (1939), however, these three conditions are all part of one disease. They state that cases of myotonia congenita if examined carefully and followed up adequately can always be shown to possess some of the characteristic features of dystrophia myotonica. On the other hand Thomasen (1948) in a review of myotonia in Denmark found five families comprising 29 myotonics whom he considered showed no evidence of dystrophia myotonica.

Our cases would seem to support Maas and Paterson. Superficially they would appear to be suffering from myotonia congenita and the age of onset would tend to confirm this diagnosis. However, two of the children show slight wasting of the thenar muscles while in both families there is evidence which is very suggestive of dystrophia myotonica.

The matter is of importance as regards prognosis. It is usually stated that dystrophia myotonica carries a grave prognosis and in Denmark it is recommended that sufferers from this complaint should be sterilized. However, if it is accepted that Family A above are, in fact, suffering from dystrophia myotonica it will be seen that the prognosis is not necessarily as grave as is sometimes supposed.

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Idiopathic Pulmonary Hæmosiderosis.—L. G. Scott, M.R.C.P. (for P. R. Evans, M.D., F.R.C.P.).

A. W., male, aged 9 years. Parents not cousins. Only child. Not been abroad. 20.9.49: Admitted to hospital because of his pallor.

Family history.—Mother died May 1949 from "multiple cerebral tumours". Father has lived abroad many years, had amœbic dysentery, bilharzia and malaria, but well now except for occasional attacks of malaria.

Past illnesses.—Aged 2 years: whooping cough. Aged 7 years: Intermittent bouts of diarrhœa for about six months. Watery yellow stools without blood or mucus. Attacks seemed to be precipitated by excitement. (No attacks for past two years.) A blood-count at the time was said to have shown a slight anæmia.

Personal history.—Appears to have developed normally; intelligent boy.

Present illness.—Always pale. Early this year became more than usually pale and developed a non-productive cough and some pyrexia. No acute dyspnœa or cyanosis. X-ray on 4.2.49 showed mottled opacities at both bases and the left mid-zone (Fig. 1). (Sanatorium treatment suggested.) After six weeks made a seemingly good recovery and was sent to boarding school in Sussex.



FIG. 1. 4.2.49

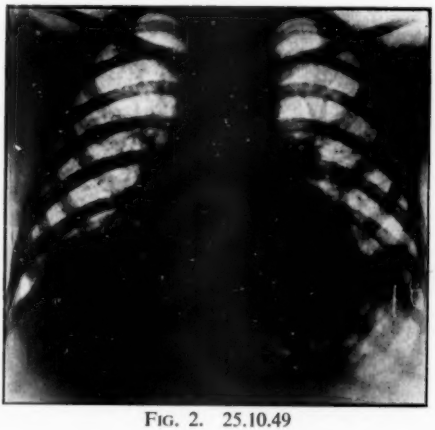


FIG. 2. 25.10.49

Middle of August 1949 began to get breathless on exertion. On return to school in first week of September noticed to be unduly pale. No cough. No bleeding. Put to bed and had slight pyrexia which subsided after a few days. Blood examination showed considerable anæmia, and X-ray on 20.9.49 showed a fine reticulation at both bases. Admitted to Guy's Hospital on 20.9.49.

On examination.—Well-nourished, pale, ginger-haired boy, with freckles. Medium-pitched systolic murmur heard all over præcordium, persistent in all phases of respiration and with change of posture. Pulse 90 regular. B.P. 110/70. Tip of spleen palpable. Liver 1½ f.b. below costal margin. Other systems N.A.D.

Chest X-rays.—4.10.49: Fine reticulation at both bases. 21.10.49: Mottled opacities appearing at the bases. 25.10.49: Marked increase in basal opacities (Fig. 2). 28.10.49: Rapid improvement. Mantoux 1 : 1,000 negative; 1 : 100 positive. Blood-count: Hb 52%; R.B.C. 3,200,000 per c.mm. C.I. 0·8. Marked anisocytosis and irregular anisochromia; moderate poikilocytosis. No nucleated red cells. Reticulocytes 8%. W.B.C. 4,700 per c.mm. (P. 40%, L. 50%, E. 6%, M. 3%, B. 1%). Polymorphs show no right or left shift. Lymphocytes mainly small type. Platelets 280,000 per c.mm., morphologically normal. Sternal puncture: Marrow shows granulocytic left shift with eosinophilia. Bleeding time normal. Clotting time at 37° C., 2 min. (normal 1¼ to 1¾ min.). Twenty-four hour urine quantitative urobilinogen estimation—less than 1 mg. (vol. 455 ml.), a low normal value. Van den Bergh, direct, negative. Serum bilirubin 0·2 mg. per 100 ml. Serum non-hæmin iron: 55 mg. Fe per 100 ml. serum (a low figure). Red-cell fragility: Hæmolysis: commenced 0·44% saline, complete 0·3% saline. Occult blood in stool: two specimens showed weakly positive guaiac and benzidine reactions. Donath-Landsteiner test for hæmolysins negative. W.R. and Kahn negative.

Urine: No iron detected. Arm-tongue circulation time 8 sec. Stool: No ova or parasites. C.S.F. normal. E.E.G.: Suggests epilepsy. No sputum could be obtained.

Progress.—24.10.49: Developed pain below right costal margin. Temperature rose to 103·8°. Not acutely distressed and no cough. No cause found for pyrexia except lung changes. Diminished movement and impaired percussion note at the right base and fine crepitations at both bases on 25.10.49 (X-ray Fig. 2). Given penicillin. Had a generalized epileptic fit on 25.10.49. No abnormal neurological signs. 29.10.49: Had a further bout of pyrexia associated with headache and stiffness of the neck. Rapid recovery from this. Received iron therapy from 11.10.49. Blood-count on 26.10.49 showed little change.

Cortical Hyperostosis.—J. SAKULA, M.D., M.R.C.P., D.C.H.

Thomas W., born 2.1.49. Normal birth and neonatal period. Birth-weight 8 lb. 4 oz. Mother W.R. negative and Rhesus negative. Child Rhesus positive. Fed on National dried milk.

Admitted to Central Middlesex Hospital, aged 3½ months, as a possible case of syphilitic osteitis of the right forearm, with pain, swelling and lack of movement for about one week.

On admission.—Well-developed child. Weight 12 lb. Right forearm swollen and tender with pseudoparalysis. Head looked large because of swollen lower jaw (Fig. 2, *see* opposite for figures) and he also had palpable thickening of both clavicles. There was no enlargement of lymphatic glands and spleen not palpable.

X-rays showed widespread involvement of skeleton, the distribution and character of the lesions being typical of Caffey's original description (*see* Fig. 1 and radiographs A – E, Fig. 3).

Other investigations.—Blood W.R. negative. Patch test negative. Blood-count—Hb 55%; W.B.C. 27,800 (49% neutrophils). B.S.R. 44 mm in one hour. Serum calcium 9·3 mg., inorganic phosphate 3·4 mg., alkaline phosphatase 38·4 units, per 100 ml. Antistreptolysin titre 10 units per ml. Biopsy not done.

Progress.—He was pyrexial for over six weeks. His marked anæmia gradually improved, but there was a persistent leucocytosis. The B.S.R. returned slowly to normal.

The affected bones showed: (*a*) Tender swelling of the deeper overlying soft tissue. (*b*) X-ray signs increased at first, then subsided over a period of four to six months. (*c*) Some swelling and tenderness persisted over the affected bones.

There were no constitutional symptoms throughout the course of the disease and the weight increased steadily.

No special treatment was given.

Pyonephrosis in "Third" Kidney with Ureter Opening into Urethra.—A. C. WILSON, O.B.E., M.B., Ch.B. (for J. C. YATES BELL, F.R.C.S.).

J. S., first seen aged 1 year 7 months. Twin girl; 8 months' pregnancy; normal labour; birth-weight 4 lb. 10 oz. Breast-fed 3/52 then Nestlé's Milk.

Admitted Fever Hospital with gastro-enteritis, aged 3 months. Transferred from there to Queen Mary's Hospital for Children, Carshalton, 30.4.48 as ? developmental defect, at 15 months of age.

Presenting symptoms and signs.—Anæmia, marked anorexia, vomiting, constipation, failure to thrive; weight aged 15 months, 9 lb. 14 oz.

On examination.—Small, thin, pale, weak child; large distended abdomen; masses in L.I.F. extending across lower abdomen; two small masses in R.I.F. ? fæcal.

Progress and investigation.—Unsatisfactory. 1 lb. gain in weight in three months. Marked anorexia, vomiting once to thrice daily, sometimes projectile. Abdominal distension a sustained feature with masses nearly always palpable before washouts.

(*continued on* p. 244).

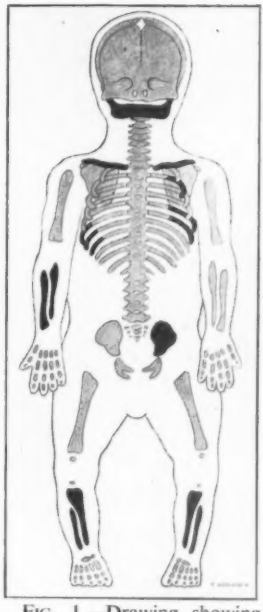


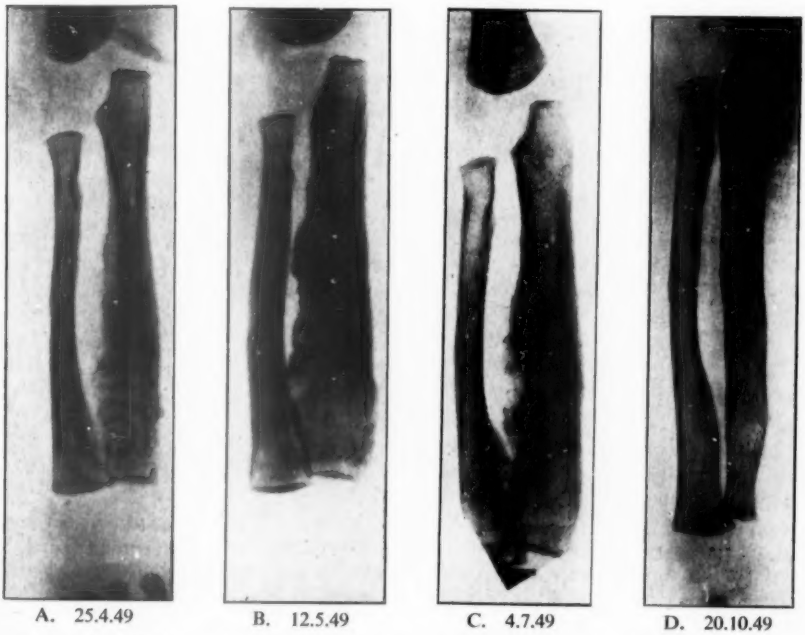
FIG. 1.—Drawing showing the skeletal distribution of the lesions.



FIG. 2.—Photograph of the child showing the enlarged jaw.



FIG. 3E. 31.5.49



A. 25.4.49 B. 12.5.49 C. 4.7.49 D. 20.10.49

FIG. 3.—X-rays demonstrating: (*a*) The character of the lesion and the process of healing in the right forearm (Films A, B, C and D). (*b*) The layered periosteal reaction as shown in the fibula (E).

Cortical Hyperostosis.—Dr. Sakula.

(*continued from* p. 242)

Constipation relieved only by enemata, washouts, &c. Symptoms became suggestive of megacolon but no response to prostigmine. Washouts results became increasingly bulky. Continued anæmia, even following blood transfusions.

Hb averaged 47–54%. White cells averaged 7,000–10,000; normal proportions for age. Blood urea 35 mg. %. Repeated specimens of urine N.A.D. Fæcal fat prior to admission 47·7 grammes %, increasing to 62·2%. Barium enema, at 16 months of age—nothing definite (Fig. 1). At 18 months of age a swelling became



FIG. 1.—Barium enema at 16 months. Abdominal distension, otherwise nothing of note.



FIG. 2.—19 months—sinus pyelogram shows dilated upper half of the right kidney with dilated ureter to bladder and a small sinus (? prolongation of ureter) to the urethra. Abdominal distension.



FIG. 3.—19 months—Left retrograde pyelogram normal. Abdominal distension.

palpable also above R.I.F. Barium meal at 18 months of age (postponed due to intercurrent chest infections) showed gut displaced to left. Average T.P.R. 97·8°, 126, 36.

At 18 months (Mr. Yates Bell): Mass in abdomen diagnosed as probably a large right renal swelling ? hydronephrosis.

Cystoscopy: Normal bladder and ureteric orifices. Right ureter catheterized at 10 cm.; good dye excretion from right ureteric catheter. No pus in bladder. Gush of pus from urethra on pressure over abdominal wall, and examining finger in rectum, i.e. *Diagnosis*: Pyonephrosis in "third" kidney with ureter opening into urethra.

First operation.—Nephrotomy. Right lumbar incision; large kidney (normal exterior) incised; purulent, stinking urine evacuated; heavy mixed growth of staphylococci, coliform bacilli and pneumococci. Tube inserted for three months.

Sinus pyelogram showed dilated upper half of the right kidney with dilated ureter to bladder and a small sinus (? prolongation of ureter) to the urethra (Fig. 2). Left retrograde pyelogram normal (Fig. 3).

At 21 months: *Second operation.*—Right nephrectomy (Mr. Yates Bell); hemi-nephrectomy was found impracticable.

On section ureteric mass contained two ureters, one dilated and passing to upper pole, one normal size with small area of normal tissue in lower pole.

Gained 5 lb. in weight in the three months following nephrectomy, and fæcal fat, which had been 62 grammes % before operation, fell to 19 grammes.

Child discharged home plump and well. Hb 60% but steadily increased to normal; now 80%. Stature of child still small but improving.

Present condition (*aged 2 years 9 months*).—Weight 23 lb. 3 oz. Height 27½ in. Fæcal fat 22 grammes %.

Comment.—Case of special interest because of long medical history with normal white cell count, apyrexia, absence of abnormal urinary signs and rapid recovery following nephrectomy. A discharge apparently from the vagina had very occasionally been found on insertion of the rectal tube for washouts. This discharge contained the same organisms as were found in the kidney.

Repeated respiratory infection due to debility of child and abdominal distension ceased following operation.

Mr. Yates Bell commented on the importance of ascertaining before operation that the left kidney was normal, and ensuring that it was not linked with the abnormal right kidney. The child's twin had died at the age of 3 months from gastro-enteritis. Unfortunately there was no post-mortem.

? **Sarcoidosis.**—E. HINDEN, M.D., M.R.C.P.

John M., born 14.1.48.

Was admitted to Whipps Cross Hospital on April 3, 1949. He had been ill for five days with fever, malaise and vomiting. Examination showed an acute pulmonary infection, which at first was thought to be a bronchopneumonia. Temperature subsided in twenty-four hours with sulphamerazine but the signs in his chest persisted. On 21.4.49 he contracted measles—a ward infection—from which he made a good recovery. Following this he became lively and active, and gained weight, from 18 lb. on admission to 21½ lb. on discharge on June 29. Yet the moist crackles persisted throughout.

X-ray taken in April showed the "snow-storm" usually identified as miliary tuberculosis, and this appearance has persisted unchanged till October, by which time he has gained another 5 lb.

Mantoux tests, 1 : 1,000 and 1 : 100, both negative. No family history of tuberculosis. Chronic miliary tuberculosis seems unlikely in the face of his obvious well-being and rapid growth (8 lb. in six months, in the second year of life) and the negative Mantoux tests. Sarcoidosis seems a possibility, but there have been no other manifestations, and I have been unable to find any reference to this disease in so young a child.

Chorea following Temporary Anoxia.—R. C. MAC KEITH, D.M.

[*November* 25, 1949]

Lupus Vulgaris and Primary Intrathoracic Tuberculosis.—F. S. W. BRIMBLECOMBE, M.D., M.R.C.P. (for REGINALD LIGHTWOOD, M.D., F.R.C.P.).

Boy, aged 2 years and 3 months.

Present illness.—In January 1949 developed a small red spot on his left cheek. This has grown gradually larger and has peeled on three occasions. No other symptoms ; has gained weight steadily.

Past history.—Drank unboiled milk until April 1949. In contact with tuberculous friend of family from January 1948 until March 1949.

Examination (28.10.49).—Nutrition good. Papular erythematous lesion on left cheek ½ in. in diameter showing "apple jelly" nodules. No cervical adenitis.

Lungs: Impaired percussion left upper zone posteriorly with diminution of breath sounds.

November 1949: Tuberculin jelly test strongly positive. X-ray of chest: "Considerable left hilar adenitis". E.S.R. 2 mm. in one hour. Gastric lavage (three times): No acid-fast bacilli on film or on culture.

Comment.—The association of lupus vulgaris with primary intrathoracic tuberculosis is unusual, though probably not so uncommon as the literature suggests.

The treatment of lupus vulgaris with high dosage of calciferol is now established. If given in other tuberculous conditions such as glandular or joint lesions, there is some evidence (Macrae) that high dosage of calciferol may cause an initial flare-up of the lesion, although subsequent healing appears to be accelerated.

Until further information is available, however, it would seem inadvisable to treat intrathoracic tuberculosis with such high doses of calciferol as are required in lupus vulgaris in view of the risks arising from the possibility of the initial flare-up. Further trials of high dosage calciferol in primary intrathoracic lesions perhaps with streptomycin and para-aminosalicylic acid may show such caution to be unnecessary.

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Mitral Stenosis First Discovered at the Age of 2½ Years.—GORDON HESLING, M.B., M.R.C.P., D.C.H. (for J. P. M. TIZARD, B.M., M.R.C.P., D.C.H.).

Michael M., aged 3 years, is the fifth of six children. The remaining members of the family are well and no member has had rheumatic fever. The family is in poor circumstances.

He had gastro-enteritis at 1 year and bronchitis at 2 years. He was given no vitamin-D supplements.

Admitted to hospital on 27.6.49 with a history of cough and feverishness for ten weeks. He was found to have a collapse in the right middle lobe and in the lingula. He had evidence of mild rickets. The cardiac murmur was noted on admission. The collapse re-expanded, the only unusual feature being a tachycardia (90 to 130) persisting throughout his stay in hospital, which was until 26.9.49. There was no other evidence of active rheumatism and his E.S.R. was never above 15 mm. in one hour.

The heart showed no clinical enlargment (apex beat 2½ in. from mid-line in the fifth space). Over a small area about the apex were heard a crescendo presystolic murmur continuing into the first sound, a second sound and a third sound followed by a diminuendo mid-diastolic murmur. The second sound was accentuated at the pulmonary area and was reduplicated.

The heart on screening showed an enlarged left auricle but no other abnormality. (*See* Figs. 1 and 2.)

The E.C.G. showed Q2 and Q3 to be present but was reported as physiological.

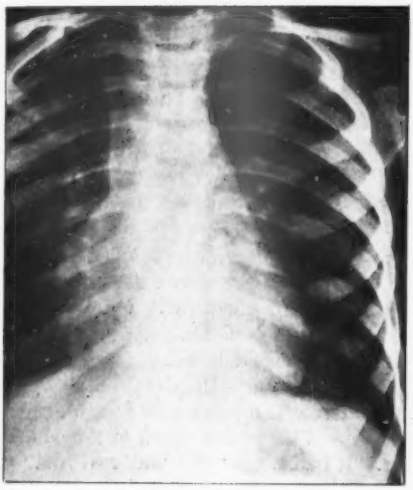


FIG. 1.—Chest, A. P. view, showing normal heart outline.



FIG. 2.—Chest, right oblique, showing indentation of œsophagus by enlarged left auricle.

Three similar cases have been found in the literature (aged at death 1 year 8 months, 2 years and 2 years 8 months), in all of which post-mortem revealed the same changes as are found in chronic rheumatic valvulitis in the adult.

In all of these cases enlargement of the left auricle was found, whereas in cases of congenital mitral stenosis of developmental origin there has been either hypoplasia of the whole of the left side of the heart (including the left auricle) or complex deformities including interventricular septal defect and patent ductus arteriosus of which, in this case, there is no evidence.

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Congenital Dermal Sinus (Connexion with Intradural Dermoid Cyst Leading to Spinal Meningitis).—J. P. M. TIZARD, M.R.C.P., D.C.H.

Diane B., born October 24, 1946.

A small punctum at the upper part of the sacrum was noticed when the child was a few weeks old. This first discharged a little caseous material on February 12, 1949, one week after a fall. The sinus had closed by February 23, 1949, but she then became ill with fever, vomiting, stiff back and later pain in the toes. From March 3 to 5, 1949, she was given sulphonamide.

On March 7 she was admitted to hospital with signs of meningitis and treatment with penicillin and sulphamerazine was begun. Lumbar puncture was repeatedly unsuccessful, but on March 10, 1949, cisternal puncture revealed a turbid yellowish fluid containing 640 white cells per c.mm. and 610 mg. of protein per 100 c.c. For the next two weeks intrathecal penicillin and fibrinolysin were administered daily by the cisternal route and the cells and protein dropped towards normal with slight clinical improvement. Culture of the C.S.F. was repeatedly sterile. On March 25, 1949, she developed measles. On March 29 the C.S.F. white cells were again raised and intrathecal penicillin treatment was recommenced. On April 2 the sinus reopened and discharged a little pus; two days later there was acute retention of urine and on the following day a flaccid paralysis of both legs. X-rays of the spine had shown no evidence of osteomyelitis but a possible spina bifida occulta of S.2.

She was then transferred to the Atkinson Morley Hospital Neurological Unit where myelography showed a complete block at the level D.4–5.

1*st Operation.*—April 14, 1949 (Mr. Valentine Logue): Laminectomy D.4, 5 and 6. Cord completely surrounded by thick yellow adherent pus. This appeared to extend cranially and caudally. It was quite impossible to introduce a catheter in either direction. The pus was removed in some areas to expose the cord which was rather thin and pale in colour with blood-vessels very shrunken.

Post-operatively there was incontinence of fæces and urine, but otherwise no change.

2*nd Operation.*—May 23, 1949 (Mr. Valentine Logue): Laminectomy L.3–S.1. Incision from spine L.2 to S.3, a portion of skin being left round the cutaneous sinus. From the skin opening a tubular sinus 2 mm. in diameter led down to a defect 1 cm. across in the second sacral laminæ. At this level the track opened up into a sac 2 × 1 cm. which was full of fluid pus and cheesy dermoid contents. The sac then narrowed to a diameter of 2 mm. to enter the dura. The dural neck of the sac was encircled and the incision extended upwards. The nerve roots were firmly bound together in hard organizing pus. The dermoid lay in the centre of the cauda equina and measured a centimetre in diameter. It had a very thin wall and had to be removed in sections. Everywhere the cauda equina was matted in a solid organizing mass.

Microscopic examination of the intradural mass confirmed that it was a dermoid cyst. Culture of the contents was sterile.

About three weeks later there was some return of power in the proximal limb muscles. She regained control of defæcation and micturition about two months after the operation. She has been home since July 29, 1949, and although there is some spastic paresis and wasting of the right leg, she can walk well.

Comment.—32 cases of congenital dermal sinus communicating with the spinal dura have been reported [1–24]. In 13 cases the sinus was connected with intraspinal dermoid cysts and in 1 case with a "teratoid" tumour [17]. 2 cases of similar sinuses communicating with subdural dermoids within the skull have also been reported [24].

There seems to be no pathological distinction between these rare dermoid sinuses and the common pilonidal sinus except for the dural connexion and this may simply be related to their localization.

In only one [8] of these 32 cases was the sinus found in the sacrococcygeal area, where the common pilonidal sinus is almost invariably found; the remaining 31 were found at all levels from the cervical spine down to the second sacral vertebra where the subdural cavity ends.

In a review [25] of 400 cases of pilonidal sinus Rogers and Dwight found no communication with the dura, but in every reported case of congenital dermal sinus above the sacral level such a connexion has existed [19].

Dermal sinuses are thought to result either from an incomplete closure of the primitive neural canal [26] or from a failure of separation of the neural crest ectoderm from the cutaneous epithelial ectoderm at the site of the deformity [7].

The theories are not mutually exclusive; the latter probably accounts for the majority of cases in which the sinus extends to the spinal meninges, without involving the cord.

However, the former must be invoked where the sinus is shown to communicate with the central canal of the cord as in one case where such a communication took place through a patent filum terminale [14].

The finding of a subdural teratoma in connexion with a congenital dermal sinus suggests yet a third alternative ætiology.

The prognosis following radical removal of the sinus (and, where present, the dermoid) is often surprisingly good even where considerable cord damage has taken

place. The aim, however, should be to eradicate any sinus above the sacrococcygeal area as soon as possible after its detection, before repeated infections have taken place.

(I wish to thank Mr. Wylie McKissock for permission to report the findings at the Atkinson Morley Hospital and Mr. Valentine Logue for his operation case notes.)

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Acute Aleukæmic Lymphatic Leukæmia Treated with Aminopterin and Blood Transfusions.—C. P. Alexander, M.B. (for Zina E. Moncrieff, M.R.C.P., D.C.H.).

D. M., female, born 26.10.45.

June 1949, feverish cold with loss of appetite. One week later, tired, pale, and showing signs of bruising easily. Severe anorexia. Admitted to hospital at Brighton.

Hb 66%; W.B.C. 8,450 per c.mm. (P. 1, L. 96, M.3%). Anæmia became worse; transfusion 350 c.c. Group O blood.

Admitted Royal Free Hospital 28.7.49: Very ill. T. 104°. Petechiæ on trunk, arms, legs and back. Subcutaneous nodules, red and raised on both legs. Bleeding from gums; tonsils infected (hæmolytic streptococci, Group A). Palpable lymph glands in cervical region, right axilla and both groins. Liver and spleen enlarged.

Hb 40%; R.B.C. 1,820,000 per c.mm.; W.B.C. 750 (polys. 5%, lymphos. 90%, 5% immature forms). Platelets 50,000. Bleeding time over half an hour.

Sternal puncture: Moderately cellular marrow, typical of acute lymphatic leukæmia. 80% of cells were of lymphocyte series, majority immature para-forms. Myeloid series absent earlier. Erythropoiesis depressed, normoblastic in type.

X-ray long bones: Typical leukæmic rarefaction at diaphyseal ends.

Urine normal.

Treatment.—Transfused with 300 c.c. Group O, Rhesus-positive blood on 28.7.49 and 5.8.49. Penicillin 1 mega unit daily in four doses from 28.7.49 to 6.8.49. Temperature normal on 4.8.49. Aminopterin 1 mg. daily in one dose for fifteen days when it was discontinued owing to toxic manifestations: (Anorexia, vomiting, severe epistaxes). Ferri et ammon. cit. grains 20 b.d. Vit. B, C and D.

Progress.—Improved after two weeks. Petechiæ, subcutaneous nodules and lymphadenopathy disappeared after four weeks.

Present condition (14 weeks after cessation of treatment).—Weight (15·2 kilos) 2 st. 5 lb. 6 oz. General condition excellent. Hb 92%; R.B.C. 4,270,000 per c.mm.; W.B.C. 8,650 (lymphos. 46, immature lymphos. 2, polys. 48, monos. 4%). Platelets 260,000 per c.mm.

Sternal puncture: 3% abnormal forms of lymphocyte series.

X-ray long bones: Marked sclerosis of epiphyses.

? **Polyneuritis: For Diagnosis.**—A. P. NORMAN, M.D. (for C. F. HARRIS, M.D., F.R.C.P.).

Brian C., aged 4 years.

History.—Admitted 26.4.49 with weakness in right leg for four months. Unable to walk or stand for two months or to sit up for six weeks.

Family history.—Seventh child. First and third children died aged 4 years from some acute cerebral hæmorrhagic disease.

Examination.—Weakness and wasting of all limbs. Reflexes diminished. Muscle tone diminished. No sensory loss. Unable to stand or sit. Circumference of skull 19¾ in.

Investigations.—C.S.F. Pressure 150 mm. R.B.C. 50. Polys. 20, lymphs. 20. Pr. 90. Chl. 770. Sugar 50 mg.%

X-ray skull normal. Mantoux 1/1,000 negative. W.R. negative.

Urine: Hæmatin and porphyrin negative. Lead 80 mg. per litre (normal).

E.S.R. 6 mm. in one hour. Blood-count normal.

3.5.49: C.S.F. Polys. 2, monos. 6. Pr. 70 mg. Sugar 57 mg. Colloidal Gold curve 000,000.

8.8.49: C.S.F. Cells 4. Pr. 100 mg. Chl. 740 mg.

20.9.49: C.S.F. Clear. Cells 8. Pr. 400. Sugar 53. Chl. 730 mg.%

18.10.49: C.S.F. (lumbar). Cells 8. Protein 450 mg.%

Blood calcium 9·3 mg.%

Progress.—Generalized flaccid paresis of all limbs. No sensory loss. Very irritable. Erythematous rash on arms. Later gradual improvement. Slight irregular pyrexia, 99–100° F. at times with diminishing frequency. Pulse 110–130.

Discharged 30.8.49.

Readmitted 20.9.49. Very irritable. Head circumference 20 in. Pupils dilated. Bilateral facial weakness. Wasting and weakness of limbs. Absence of deep reflexes. Respirations became irregular and alternately deep and very shallow with occasional periods of apnœa. Never incontinent.

Progress.—No significant change.

Congenital Indifference to Pain.—W. ROE, M.B., B.S., D.C.H. (for D. G. LEYS, M.D.).

M. P., female, born 26.7.48. Admitted hospital July 1949 for failure to gain weight, and bronchitis. Mother previously three years in mental hospital. Father high-grade defective. Child was full term, normal pregnancy and delivery. Birth-weight 9½ lb. Pneumonia at three months.

On admission.—Several indolent ulcers of hands due to the child's practice of biting her fingers. Poor nutrition, hypotonia, pallor, angular stomatitis, ulcerated tongue, rhinitis.

At 15 months this child could stand, played actively with toys, spoke no words, and although probably mentally retarded was not grossly defective. The head was small (circ. 15¾ in.). All forms of painful stimuli failed to produce the usual response; they seemed merely to amuse her. No signs were found suggesting any involvement in the rest of the nervous system, nor were there other congenital defects. Wassermann reaction negative.

Diagnosis.—Congenital indifference to pain, probably the result of cerebral agenesis.

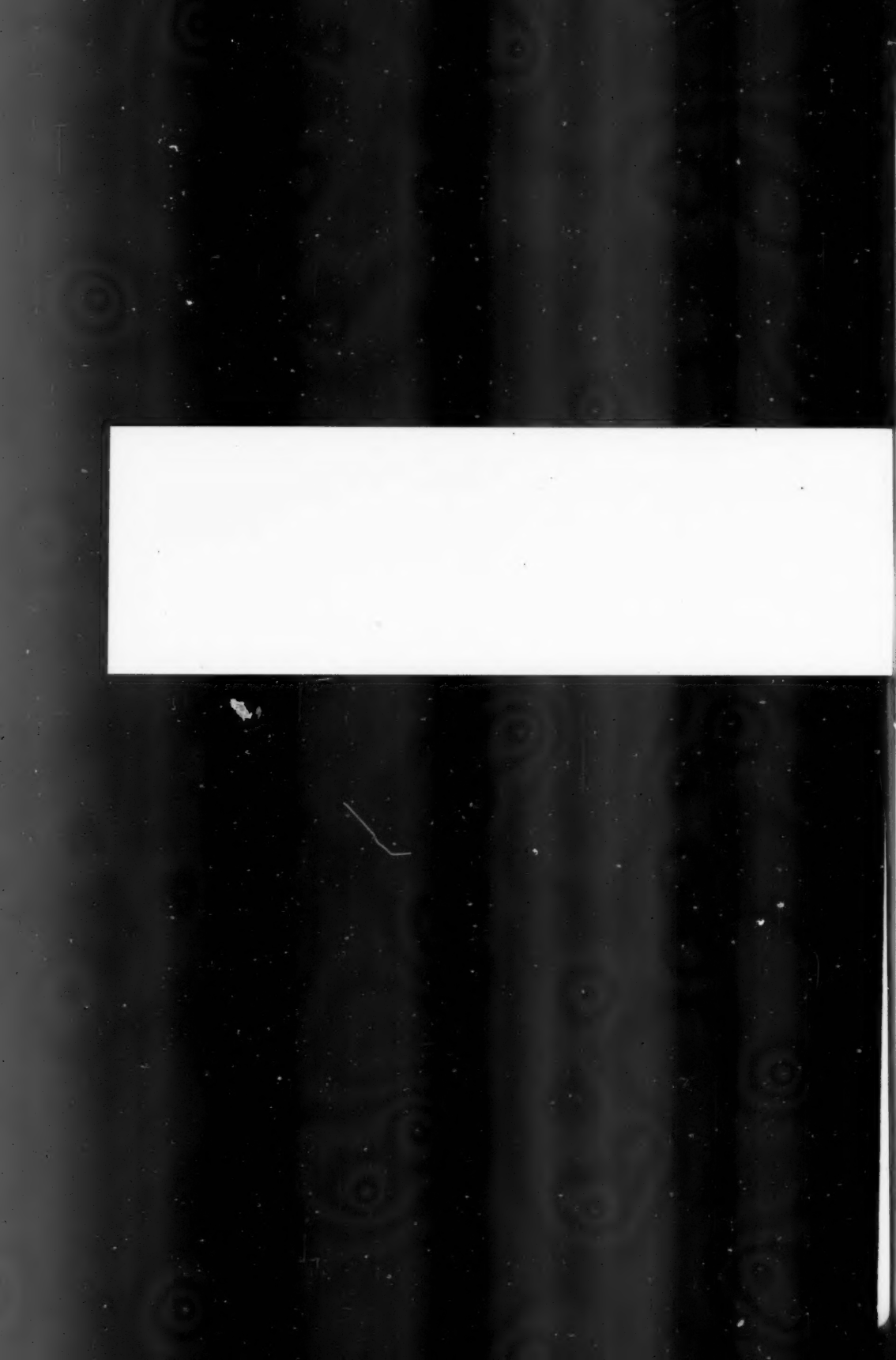
PLEASE NOTE

Section of Pædiatrics

(*October* 28, 1949)

Retrolental Fibroplasia Occurring in Twins.—J. K. MARTIN, M.R.C.P.
(*Proceedings*, **43**, 235, March 1950.)

The blood groups published with the details of the above case in the issue of March 1950 are incorrect. They were submitted in error for publication and must, therefore, be regarded as invalid, without prejudice either to the Royal Society of Medicine or to the Laboratory concerned.



Section of Neurology

President—JULIAN TAYLOR, C.B.E., M.S., F.R.C.S., F.R.A.C.S.

[*November* 3, 1949]

MEETING AT THE NATIONAL HOSPITAL, QUEEN SQUARE, LONDON, W.C.1

Juvenile G.P.I.—J. PURDON MARTIN, M.D.

B. T., girl, aged 6 years.

Complaint.—Progressive speech disturbance and dementia—for six months.

Family history.—Second child. One sister, five years older, normal.

Past history.—Normal progress up to the age of 5.

History of present condition.—Illness started with fit eighteen months ago preceding an attack of measles. A few months later progressive dementia noted with temper tantrums, sleep disturbance and speech disturbance.

On examination.—Marked retardation, labile mood, dysarthria, pupils dilated with poor reaction to light, bilateral ptosis. Plantar responses extensor.

Investigations.—C.S.F. 8 lymphocytes, protein 60 mg. per 100 c.c. Lange 5555432100. W.R. positive 4442 (20 units).

Hyperostosis Frontalis Interna and Calvariæ Diffusa with Surgical Relief of Severe Headache (also Bilateral Scalenus Anticus Syndromes).—COLIN EDWARDS, M.R.C.P.

Female, aged 48.

Family history includes epilepsy in mother, "convulsions" in childhood in a sister and obesity in both parents and a sister.

Patient's history.—Menarche at 8. Obesity always, but moderate until partially immobilized by phlebitis in legs at 31 and by cellulitis in leg and osteomyelitis of tibia at 36 when she also had 8 months' amenorrhœa. 10 stones at 21 years. 16½ stones at 38 years, obesity generalized over trunk and limbs. Headaches since a young girl and at 38 had them about once a



FIG. 1.—Shows calcification in falx, varying depth of frontal hyperostosis and right subtemporal decompression.



FIG. 2.—Shows marked internal frontal hypero stosis with deep pit. Outline of sella normal. [Diffuse hyperostosis in parietal area.

fortnight. B.P. then 160/100. At 38 C.N.S. examination was normal; C.S.F. analysis normal and blood W.R. neg. Blood calcium was 9 mg./100 c.c. and glucose tolerance curve slightly flattened. Skull X-ray (Figs. 1 and 2) showed the changes listed in the title, also calcification of falx but a normal sella.

From the age of 38 to 42 she suffered increasingly from severe intermittent headache, sometimes with vomiting and accompanied by loss of vision for twenty minutes with flashes of

light as it returned. Her visual acuity at 42 years was diminishing rapidly and her fields, normal at 38, were markedly contracted.

The picture throughout these years was complicated by a smouldering osteomyelitis in her tibia. Between 42 and 43 years of age, however, her vision deteriorated further with severe headache and vomiting. Optic foramina were radiologically normal.

A right subtemporal decompression was done in April 1944 (patient 43 years). It showed an abnormally thick, hard, brittle and vascular temporal bone with an irregular inner surface to which vascular dura was adherent at many points. For a year her headaches were much less severe. They then began to increase again and she had an attack of loss of consciousness without warning. Menorrhagia became very severe and at 45 years of age a radium-induced menopause eased the headaches somewhat. At 46 years a right scalenus anticus syndrome developed and was relieved by operation. At 47 years the headaches having grown pitiably severe, a left frontal decompression was done. It showed a thick bone with no evident diploe and with a craggy under-surface to which the dura was adherent at many points. Dura and brain were drawn up into one particularly deep pit at the frontal pole. It was stripped and the bone replaced. Relief from headache has been marked, and those which have since occurred have been dull and usually related to emotional stress. In the ten months immediately after operation she had occasional attacks of giddiness and one of loss of consciousness but for a year now headache and other symptoms have been slight.

Her B.P. has steadily risen from 160/100 to 230/120 in eleven years. She now has some features of a left scalenus anticus syndrome.

Birth Injury of Left Arm Showing Crossed Re-innervation from Phrenic Nerve into Nerves Supplying Biceps, Extensor Digitorum Communis and Other Muscles.—FRANK SARGENT, M.D.

L. C., male, aged 18 (carpenter).

Has difficulty in holding his work with his left hand because of weakness of the left arm and hand, especially wrist-drop, dating from birth. It was a difficult labour, as he was a 14 lb. baby but no instruments were used.

On examination.—Left arm: no sensory loss; absence of arm reflexes (present on the right); weakness and wasting of most muscle groups corresponding to a lesion extending from C3 to C7 inclusive. Wrist-drop is marked but the extensors of the forearm felt elastic and healthy, and once during examination there was seen spontaneous extension of the fingers, which was attributed to a trick movement using lumbricales but, in view of the later EMG findings, it may well have been due to a deep breath. The clinical impression was that the lesion was less severe than the disability suggested. No Horner's syndrome seen, but left palpebral fissure is narrower than right.

Electrical tests by Dr. P. Bauwens indicated that the only muscle severely paralysed was the left extensor carpi radialis. Needle electrodes inserted into biceps and extensors of forearm elicited spontaneous motor unit potentials in time with respiration, and when the patient was told to take a deep breath, bursts of motor unit activity were recorded.

The conclusion is that severe traction injury at birth caused tearing of nerve roots C3 to C7, and that subsequently crossed re-innervation occurred from phrenic roots to the Schwann tubes to biceps, extensor digitorum communis, &c. This would explain the apparent integrity of these muscles in spite of severe loss of power and also, of course, the effect of respiration on the action potentials.

Two similar cases of crossed re-innervation of the phrenic to muscles in the arm have previously been seen in Dr. Bauwens' clinic.

Myoclonus of Palate, Pharynx and Larynx.—A. B. KINNIER WILSON, M.R.C.P., for F. M. R. WALSHE, O.B.E., M.D.

W. C., female, aged 61.

Family history and past history.—Non-contributory.

Present illness.—Fronto-occipital headaches, almost daily at the beginning of 1948. Sudden loss of consciousness early one morning in July 1938 and has an amnesia for a month. She was admitted to St. Mary Abbots Hospital, where it was stated that she was semicomatose, had nystagmus—slow to the right, rapid to the left—right-sided ataxia of cerebellar type and dysarthria. The C.S.F. was heavily blood-stained. Later she was seen to have a divergent squint and some drooping of the left corner of the mouth. She became markedly euphoric. She had considerable vertigo on sitting up. This has gradually improved, but it is still enough to make walking difficult.

Since the ictus she has only had one headache.

On examination.—Very slight slurring dysarthria. Nystagmus in all directions, most on looking to left. Palate rises in the mid-line, but there is a constant 3-second myoclonus of both sides of the palate, pharynx and larynx. No cerebellar signs in the limbs, but gait is

wide-based and ataxic. Reflexes: right biceps diminished, right triceps and arm absent from old injury to elbow. Abdominals absent, otherwise reflexes normal in all respects. No sensory loss.

It was suggested that this was a lesion of the upper end of the central tegmental tract near the third nerve nucleus, due to a petechial hæmorrhage.

Bilateral Sacral Plexus Lesion—Polyarteritis Nodosa.—GERALD PARSONS-SMITH, O.B.E., M.D.

Man, aged 44.

Past history.—October 1948: Primary syphilis (W.R. ++; treponema isolated) treated with complete course of arsenic, bismuth and penicillin which produced normal serological reactions. 1930: Malaria. 1924: Typhoid.

Family history.—Father died of disseminated sclerosis.

History of present complaint.—May 1948: Gradual onset of lassitude and excessive malaise. 3.6.49: Sudden attack of severe upper abdominal pain lasting twelve hours; associated with fever and severe frontal headache.

15.6.49: Dull aching pain in joints of right upper limb, lasting three days. Four days later sudden onset of pain of left sciatic distribution; this improved over a period of six weeks leaving some numbness of dorsum of the foot. He continued to feel very run down and lost weight. During this period he had two attacks of very severe abdominal pain similar to his first attack.

12.8.49: Acute onset of right foot-drop with blunting of sensation over the outer side of leg. Admitted to St. George's Hospital on 7.9.49 under Dr. H. Gainsborough and Dr. J. R. Nassim, to whom I am indebted for permission to show this case. Stated he had some blurring of vision in both eyes for three days about this time.

Present condition.—Protracted fever around 100° F. Lost 2 stones in weight. Except for some generalized arteriosclerotic changes and persistent tachycardia his cardiovascular system shows no abnormality. B.P. 140/80.

Nervous system.—Cranial nerves and brachial plexus normal. Severe pain in the muscles of both legs. Both thighs are wasted, 1 in. more wasting on the right. Muscle power diminished, especially in right anterior tibial muscles. Right-sided foot-drop and weakness of right plantar flexors. Knee-jerks present, ankle-jerks absent. Patchy sensory loss in right L.5 distribution, hyperæsthesia of soles of both feet, sensation otherwise normal.

Investigations.—Blood-count: R.B.C. 3,700,000; Hb 77%; W.B.C. 17,900 (polys. 85%, lymphos. 9%, monos. 4%, eosinos. 1%, basos. 1%). E.S.R. 37 mm. in one hour. Urine: red cells and granular casts. Stools: positive for occult blood. C.S.F. normal.

Pulsometer curve shows a complete R.D. of the right tibialis anticus muscle.

I.V.P.: normal excretion.

Muscle biopsy: R.tib.ant. (Prof. Theo Crawford): Endarterial proliferation of the small vessels with perivascular collections of inflammatory cells. In places there is fibrinoid necrosis of the media, and the picture is characteristic of polyarteritis nodosa.

Comment.—The sudden occurrence of the neurological symptoms in the lower limbs exemplifies the vascular basis of the peripheral neuritis in polyarteritis nodosa.

Boeck's Sarcoidosis of the Nervous System.—DENIS WILLIAMS, M.D.

G. M., male, aged 39. Bank clerk. Married, with two healthy daughters. Family and previous medical histories are not contributory.

History.—The patient was in excellent health until May 1948 when his left arm became clumsy. Two months later, attacks of extensor rigidity in left leg began on climbing stairs. These symptoms persisted virtually unchanged until June 1949, although he had two attacks of loss of consciousness lasting some hours in December 1948 and April 1949, the latter preceded by a motor dysphasia. In June 1949 his left leg began to go into rhythmic clonus, in attacks lasting twenty to thirty seconds and followed by transient weakness. Two months later he experienced two types of attack: one in which he suddenly fell backwards recovering immediately; the other of clonic movements simultaneously affecting the left face, arm and leg without alteration of consciousness. He had no cough, his weight was steady, there were no skin lesions and he had no symptoms referable to other systems.

On examination.—The patient was normal mentally, and his intellectual performance was average but was not thought to be up to the expectation for a man of his background.

The cranial nerves were normal except for a slight pallor of the right optic disc. There was a mild left hemiplegia, involving arm and leg equally with slight increase in all tendon reflexes and an extensor plantar response. The abdominal reflexes were symmetrical. There was inco-ordination falling away and rebound, with an irregular intention tremor on the left side, as well as the hemiplegia, and it was clear that he had a combined cerebellar and pyramidal lesion on that side. Sensation was perfectly normal.

Heart normal, B.P. 150/90.

No abnormal signs were found on examination of the chest and there were no enlarged glands.

Very frequent attacks involving the left side of the body in tonic and clonic movements were observed in hospital. They lasted for about ten to twenty seconds and included a slow tonic contraction of the arm outwards and upwards.

Investigations.—Blood-count: R.B.C. 5,410,000 per c.mm.; Hb 116%; C.I. 1·07; W.B.C. 4,000 per c.mm. (polys. 62, lymphos. 34, monos. 1, eosinos. 3%).

E.S.R. 1 hour 5 mm., 2 hours 13 mm.

Blood proteins: Total protein 7·35 grammes %. Albumin 3·4 grammes %. Albumin: Globulin 1 : 1·16.

Cerebrospinal fluid: Pressure 180 mm. Free rise and fall. Clear and colourless. Cells—none seen. Protein—0·07 gramme %. Nonne Apelt weak positive. Pandy positive. Lange—0001110000.

W.R. negative in blood and C.S.F.

Mantoux reaction negative 1 : 10,000 and 1 : 1,000. No tubercle bacilli were seen in repeated examination of sputum, and in culture of gastric washings.

The electro-encephalogram was recorded on two occasions in Nottingham, where it showed epileptic discharges and a focal abnormality in the *left* temporal lobe. These observations were confirmed. The report (18.10.49) read "The E.E.G. is abnormal and repeated epileptic discharges occurred. These appeared to arise in the *left* hemisphere with occasionally a phase reversal in the temporal aspect of the frontal lobe, somewhere about the Sylvian point. This observation is the same as that which was made earlier at Derby. I cannot find any evidence of a right-sided parietal lesion to account for his left-sided tonic attacks."

X-rays of the chest (18.10.49) were reported upon as follows: "There is an irregular coarse mottling present in both lung fields and both hilar shadows are prominent. The appearances are unusual and are consistent with sarcoid changes. There is pleural thickening in the lower part of the oblique fissure." Previous X-rays reported upon in Derby in the summer had led to the diagnosis of Boeck's sarcoidosis.

Ventriculography carried out on two occasions by Mr. Clark Maxwell in Derby showed a normal ventricular system.

X-rays of the hands showed small cyst-like areas in the heads of both first metacarpals.

Liver biopsy was contemplated but was not carried out owing to the high level of the liver dullness.

There was general agreement that the clinical picture and the X-ray appearances were those of sarcoidosis. In the central nervous system lesions were present in both cerebral hemispheres, as shown by the attacks, the hemiplegia, and the E.E.G. abnormalities; in the left cerebellar mechanism, and probably also in the right optic nerve. Involvement of the central nervous system in Boeck's sarcoidosis is uncommon but has been described on several occasions.

Hereditary Perforating Ulcers of the Foot.—REGINALD KELLY, M.D., for DENIS WILLIAMS, M.D.

E. P., aged 24.

Family history.—Younger brother, mother and maternal uncle, maternal grandmother and great-aunt all suffered from the same disease.

Enuresis until the age of 15. First ulcer appeared at age of 21; since then recurrent, usually painless, penetrating ulcers on under-surface of both great toes, right third toe and right fifth toe with osteomyelitis of the proximal and terminal phalanges of the right big toe. No abnormalities of sensation or gait noticed by patient.

On examination.—Both big toes are enlarged and indurated, right more than left. On both there is a deep ulcerated area, punched out and dry on the left, ragged with a dirty, wet slough at the base on the right, with no normal granulation tissue. The ulcers are painless and there are similar ulcers of the same dry type as the left on the third toe of the right foot.

Loss of all forms of sensation on periphery of both feet with secondary level in stocking distribution on both legs up to mid-calf level below which there is a mild impairment of sensation. Pathological sweating at level and distal to both ankles; a flair reaction is obtained within the area of sensory impairment. Tendon-jerks preserved but ankle-jerks considerably more sluggish than knee-jerks.

Investigations.—X-rays: Spine, no abnormality; feet, osteomyelitis of proximal and terminal phalanges of right big toe.

C.S.F. normal. W.R. negative. E.M.G.: the small muscles of the medial border of the soles of both feet and the left tibialis anticus were examined; only normal voluntary action potentials were seen, there was no spontaneous activity and nothing to suggest a lower motor neurone lesion in the feet.

Section of Obstetrics and Gynæcology

President—LESLIE WILLIAMS, M.D., M.S., F.R.C.S., F.R.C.O.G.

[*December* 16, 1949]

DISCUSSION ON STRESS INCONTINENCE OF URINE IN THE FEMALE

Mr. Charles D. Read (London): In this Discussion we shall consider stress incontinence only. It is emphasized that the subjects of urge incontinence and the incontinence associated with neurological lesions are excluded.

The exact mechanism of stress incontinence is not completely known. It would appear that the nerve supply to the sphincter mechanism is intact, but it would also appear that when the bladder neck descends on straining, this bladder-neck control mechanism becomes defective. The evidence is overwhelming that the actual urethra itself plays little part in control. Terence Millin demonstrated this bladder-neck descent in a series of cystographic studies, and, furthermore, cystographic post-operative studies of operatively cured cases reveal little or no bladder-neck descent.

The structure supporting the bladder neck appears to be the pubo-cervical musculofascial layer and there is evidence that the tone of the pubo-coccygeus portions of the levatores ani muscles exerts an important influence on this descent. Kegel has suggested that on occasions the pubo-coccygeus muscles are denervated by the over-distension produced by the passage of the fœtal head. This over-distension is especially evident when the fœtus is large and when the occiput is posterior. He suggests that the inelastic nerve fibres to the muscles are damaged with resultant defective nerve supply of a variable percentage of muscle fibres of the pubo-coccygeus muscles and his new ingenious instrument—the perineometer—is designed to enable the patient to increase levator tone by active contractions against the instrument. The perineometer consists simply of a rubber obturator which fits the vaginal canal. The obturator is connected to a manometer of large excursion and active levator exercises are instituted for ten minutes thrice daily over a period of three weeks. It is really a form of physiotherapy. For the first week there is usually little impression on the manometer, but, with persistence, variable pressures are registered, and by the end of three weeks the manometer registers usually anything between 60 and 100 millimetres of mercury pressure. The instrument is especially useful in recent post-partum stress incontinence. It is obviously an instrument for use in cases associated with genital relaxation rather than prolapse. It does not cure all cases, but is worth a trial in all recent post-partum patients and in those with moderate relaxation. If the patient exhibits a demonstrable utero-vaginal prolapse, surgery is obviously indicated.

It can be accepted that in cases of prolapse with or without incontinence treated by the routine Manchester procedure or by vaginal hysterectomy and repair there is a relatively high cure rate of the prolapse with a relatively low cure rate of the incontinence, and it is essential to implement either method of surgical treatment by some special procedure directed towards the cure of the incontinence. The Marion, Kelly and Bonney procedures of sub-urethral repair will cure some, but by no means all of these patients, and various observers have assessed the cure rate of these procedures as between 75% and 95%. Our experience is that the lower figure is the more accurate. Kennedy and Joshua Davies of

the Women's Hospital, New York, use much more extensive procedures with wide and free exposure of the urethra, bladder neck and base, and a careful fascial repair, and they report a 90% cure rate. Reddington of London uses a series of simple mass ligatures after the free exposure and mobilization of the urethra and bladder neck, the effect of which is to elevate and fix the bladder neck at a much higher level.

Pacey, after a wide dissection and mobilization and a careful fascial repair, approximates the medial borders of the pubo-coccygeus muscles in addition. Ingelman-Sundberg of Sweden divides the pubo-coccygeus muscles and actually crosses them.

It may here be pertinent to mention the distressing cases of stress incontinence which persist after an otherwise successful repair of a vesico-vaginal fistula which has involved the bladder neck. At the time of repair, after closure of the fistula, attempts should be made to attain elevation and fixation of the bladder neck. These attempts are often not completely successful owing to paucity of surrounding tissue and tension. Subsequent vaginal repairs tend to be hazardous, and sling procedures perhaps more so in that there is the danger of re-opening the fistula. Wilfred Shaw has recently suggested the interposition of the bulbo-cavernosus muscles as in the Martius technique in such cases.

Of all the purely vaginal operations, my small experience of the Pacey operation has convinced me that in my hands this is the most effective procedure I have yet employed by the vaginal route.

Whatever method be employed there will remain a residuum of failures of cure by the vaginal route, and these failures constitute a fascinating and interesting group. The choice of treatment lies between a repeat vaginal attempt and some more extensive procedure involving a purely abdominal approach or a combined abdomino-vaginal approach.

The Aldridge and Studdiford operations are the best known of the combined abdomino-vaginal sling procedures, and I have reserved these for patients in whom there has been a recurrent cystocele with severe incontinence after an otherwise successful repair for utero-vaginal prolapse.

Perrin of Lyons and Everard Williams of London have advocated bladder-neck suspension to the periosteum of the back of the pubis and report good results. Marshall, Marchetti and Kranz of New York have described cervico-cysto-suspension by the abdominal route.

Wilfred Shaw has advocated the insertion of a fascial sling suspending the bladder neck and urethra by a strip of fascia lata supported above by the pubic bones, which are drilled for the purpose.

My own interest in the failed vaginal group has been in the Millin retropubic sling operation, which is a purely abdominal retropubic procedure using aponeurotic straps from the abdominal wall.

To June last I performed 126 Millin sling operations; the results are as follows:

TABLE I.—AGE INCIDENCE

30–40	11	Total, 126
41–50	46	
51–60	59	
61–70	10	

Youngest patient 35 years
Oldest patient 65 years

TABLE II.—RESULTS IN 126 OPERATIONS

Absolute cure	91
Partial cure	21
Failure	13
Operative deaths	1

(Pulmonary embolus 10th post-operative day)

TABLE III.—CAUSES OF FAILURE

(1) Insufficient elevation of bladder neck	8
(2) Severance, by sling, of urethra from bladder neck	1
(3) Diffuse retropubic sepsis	3
(4) Massive retropubic hæmatoma	1

To sum up the position as I see it at present, to cure stress incontinence, elevation and fixation of the bladder neck are the prime necessities. In certain cases of recent post-partum incontinence with mild degrees of genital relaxation some may be cured, or at least improved, by the use of the perineometer.

If surgery be embarked upon the primary procedure should be a purely vaginal one, and it must ever be remembered that the first attempt should be the successful one, and consequently it should be adequate. In the failed vaginal case some more extensive procedure is indicated, and it would appear that some form of sling operation offers a reasonable hope of cure.

I hazard the opinion that Mr. Millin's latest sling operation from its simplicity and effectiveness will make these more extensive sling procedures unnecessary.

I close with the conviction that a sling operation is rarely justifiable as a primary procedure, and must be reserved for use after failure of cure by the vaginal route.

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Professor J. Chassar Moir: *The Aldridge sling operation.*—Some four years ago, in 1945, I found myself championing the cause of the Aldridge sling operation before this audience and comparing it, pro and con, with the Millin sling operation; later (1947) I pursued the subject further before a meeting of the Edinburgh Obstetric Society.

My views on these operations remain substantially unaltered. The end-results of both are very similar, and the choice of either depends on the opinion of the surgeon regarding the ease and safety of the respective techniques. In favour of the Aldridge operation one can say that the important dissection round the upper urethra is done by direct approach, and by a route familiar to the gynæcologist; there is therefore comparatively little danger of serious injury to urethra or bladder. In favour of the Millin operation one can say that the approach is entirely by one route—the abdominal—and that the operation can be performed quickly and without need for altering the patient's position throughout. In making his choice, much will depend on the experience of the operator with the type of technique used. I feel bound to say, however, that a surgeon new to this class of work is likely to get good results with less risk to his patient if the Aldridge technique is selected.

Comment on the ingenious Millin No. 2 operation now presented is idle until we have had experience. Meantime let us congratulate Mr. Millin on his enterprise, and on having—in more senses than one—broken new ground.

As previously emphasized, I hold that sling operations of any variety should be reserved for those cases in which simpler surgery has failed to effect a cure—the case in which the surgeon, so to speak, has "worked his thunder," but in which stress incontinence of urine continues as before. In consequence of this conservative attitude I and my assistants, Mr. Scott Russell, Mr. Gordon Lennon, and Miss J. R. C. Burton-Brown, have performed the Aldridge operation (or some simple modification) on only 26 cases to date. It should also be mentioned that many of these operations have been done on very unpromising material. For many years I have had a special interest in vesico-vaginal fistula work, and have had a great many "intractable" cases of this injury sent from various parts of the country. Some of these patients have suffered extensive destruction of the upper part of the urethra and the sphincteric region of the bladder; and although in every case the fistula has been closed, stress incontinence of varying degree has sometimes persisted. Some of these patients have later been treated by the Aldridge operation; and in judging the results presented in the following table allowance must be made for this particular type of case, which in no circumstances can be classed with those in which the bladder and urethra are anatomically normal.

ALDRIDGE SLING OPERATIONS
Total—26 Cases

	No vesico-vaginal fistula	Vesico-vaginal fistula
Highly satisfactory	11*†	7
Substantially improved	1	1
Moderately improved	1	2
No change	1‡	2

* One patient untraced; when seen four weeks after operation the result was excellent.
†One patient, an elderly woman, died three months after operation. Multiple pulmonary and coronary emboli found; operation site free from any evidence of sepsis.
‡ Not a case of true stress incontinence.

Nine of the 26 patients cases were observed for periods of three to six years; there was no relapse of symptoms. One gets the clinical impression that if improvement is maintained for six months, the effect is permanent.

In conclusion, let me again stress the fact that the Aldridge technique, although somewhat time consuming, is simple, and is free from high risk of damage to bladder or urethra. In suitably chosen cases this particular form of sling operation can give excellent results.

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Mr. Terence Millin (*Abridged*): The spate of "new" operations, which have flooded the journals during the past few years would appear to indicate a not untimely recognition of an ill-founded complacency with past results.

In 1946 Mr. Everard Williams stressed the necessity for urological and neurological investigation in all cases (*Proc. R. Soc. Med.*, **40**, 361). How often, even to-day, is that excellent precept carried out?

The problems before us are (*a*) how to prevent or minimize the incidence of the "failed case"? and (*b*) how to deal successfully with it, should it occur?

Everyone is agreed that if genital prolapse or evidence of marked pubo-cervical relaxation is present then some form of vaginal repair should be undertaken, at least in the first instance. Whether such should be perpetrated as often as five times, as was the case in 3 of our patients subsequently cured with a sling, seems doubtful. At the risk of being held presumptuous, I must say that I cannot but believe that a more careful urological study of these cases pre-operatively along the lines we shall suggest in a few moments might indicate a group which would be helped by an additional buttressing—Aldridge sling if you like—added to the repair. I should also like to go on record as being sceptical of lasting results in the Pacey-Treahy procedure where the approximation of pubo-coccygei is under extreme tension. (Slides illustrating the speaker's objections were then shown.)

Still on a destructive note, may I say a few words about some other methods in use to-day. The various "sling" techniques—Goebell-Stoeckel, Aldridge, Studdiford, Delinotte, Marshall and our own—have now been practised sufficiently long to have established that the *principle* will give satisfactory results provided that the technique has been correctly performed and that no post-operative infective phenomena have intervened. Faulty technique is by far the commonest cause of failure. Too often undue elevation of the bladder neck transforms a case of stress incontinence into one of absolute or relative retention. Too often a faulty passage of the sling occurs and cases have been met where it has been passed through bladder, urethra or vagina. The retropubic type of operation, whether it be Marshall's or mine, would appear to be unduly difficult for many operators particularly when they are infrequent explorers into the cavum Retzii.

The "sling" operations carried out *per vaginam*, such as the Aldridge, would seem to be more readily performed by most gynæcologists but these are not immune from occasional distressing sequelæ such as infection carried into the *undrained* retropubic space from an infected vagina. It is also theoretically undesirable to have the unabsorbable strap sutures in close proximity to the vaginal suture line.

Of the recently advocated "bone-boring" procedure, the consensus of opinion is that it is one of the most ill-conceived surgical procedures in living memory. To maintain that swabbing of a cavity so commonly infected as the vagina with any known antiseptic can render it a fit area through which to open up cancellous bone with its well-recognized poor resistance to infection, even in these days of antibiotics, would seem to be abject heresy.

The Everard Williams procedure, little more than a substitution of catgut for the silk employed in the Perrin cervico-cystopexy, which has not given lasting results, at least on the Continent where it has been tried extensively, does not appeal to many.

Now to attempt to be constructive. Before planning an operation for the relief of severe stress incontinence it is surely essential to be fully conversant with the exact pathology present. The degree of pubo-cervical relaxation, as is well known, bears no relationship to the extent or even presence of urinary loss. One ought to know the precise dysfunction of bladder and urethra, and I believe that this cannot be assessed sufficiently accurately by clinical means but can be readily demonstrated by our vertical cystographic technique already described elsewhere [1].

May I remind you briefly of the commonest urological abnormalities found in our cases?

(*a*) "Funnel" deformity of the vesical outlet: (i) Congenital, (ii) Neurogenic, (iii) Post-operative.

(*b*) Ptosis of the bladder neck on raising the intra-abdominal pressure.

(*c*) Loss of the normal anterior concave curve of the urethra.

(*d*) Abnormal dilatation of the whole urethral canal.

(*a*) I shall not consider the problems of treatment in the first two groups as they are of urological rather than gynæcological interest. The third group, however, is an important one in that it includes those cases of stress incontinence developing after a successful closure of a trigonal vesico-vaginal fistula. The reason is not far to seek; the cure not so simple. Either subsequent vaginal interventions or a retropubic sling may jeopardize the scar of the healed fistula. I submit that our new sub-pubic sling may be the answer.

(*b*) Cystography will demonstrate in a high proportion of cases the vesical neck descent on raising the intra-abdominal pressure by coughing, &c. Some care is necessary in interpreting these cystograms.

(*c*) The oblique view of the vertical cystogram will frequently reveal a loss of the urethral curve—a point noted clinically many years ago by Victor Bonney.

(*d*) Marked urethral relaxation is revealed by loss of the opaque medium alongside the No. 20 Ch. catheter commonly used for the cystogram.

The latter two abnormalities may not be common but I have 3 personal cases where an Aldridge sling operation performed elsewhere had failed to cure the incontinence, though supporting the bladder neck, and in whom a simple correction of these by our sub-pubic approach gave an excellent result.

Sub-pubic Approach to the "Failed Case"

I shall now describe my sub-pubic approach to the problem of the "failed case" where no marked pubo-cervical relaxation is present. It would appear to have the merit of simplicity, both for patient and operator. It still retains the "sling" principle when a descent of the bladder neck has been shown to occur and at the same time allows us to correct, if present, the loss of the urethral curve and an undue laxity of the urethral canal.

The operation briefly consists in passing a sling under the bladder neck by a sub-pubic approach. The sling has, to date, consisted of a 20 cm. strap of fascia lata obtained either by means of a stripper or by a deliberate incision. In all probability a similar length of stout kangaroo tendon or similar material would suffice. Having obtained the strap, the patient is placed in the lithotomy position and whilst the operator is working below an assistant makes a short 5–8 cm. transverse incision above the pubis to expose the anterior rectus sheath. A No. 20 Ch. 5 c.c. Foley catheter is passed along the urethra and the balloon dilated to capacity. The bladder is allowed to empty and the balloon drawn down until it impinges against the vesical neck. A short incision is now made between clitoris and external urinary meatus, closer to the latter, and deepened for $\frac{1}{2}$–1 cm. until the inferior leaf of the urogenital diaphragm is met. A few veins of Kobelt's plexus will be sectioned. The hiatus through which the urethra emerges will be clearly seen and this is now enlarged by passing a closed pair of Mayo's scissors along the dorsal surface of the urethra into the hiatus and then opening the blades. The right index finger is now passed through the hiatus deep to the sub-pubic arch into the retropubic space and the bladder neck pushed back gently from the pubis. If the venous ooze is troublesome a temporary small pack is placed deeply whilst the sling is placed sub-urethrally. The operator's left forefinger, ensheathed in a sterile finger-cot is placed in the vagina and pressed forwards, so presenting the urethra with its contained catheter into the field. A Morley's hernia needle or Millin-Read forceps is now gently insinuated under the urethra immediately below the bladder neck (identified by the balloon of the catheter), the jaws are slowly opened so creating the tunnel. One end of the strap is seized and drawn through. Utilizing a Bozeman's uterine packing forceps each end of the strap is passed into the little

wound deep to the pubis, traversing the retropubic space and corresponding rectus muscle and made to present against the overlying aponeurosis. The assistant makes a small buttonhole incision in the sheath and seizes the end of the strap with a pair of Kocher's forceps. Each end of the strap is then drawn upon avoiding undue tension. It must be stressed that, as in all sling operations, the aim is *not* to elevate the bladder neck but rather to prevent its descent when the intra-abdominal pressure is raised. By means of two chromic catgut sutures the two cavernous bodies are drawn together anterior to the urethra so restoring its normal curve and the little incision in the fourchette closed by means of 3 fine catgut sutures. If the urethra has previously been shown to be unduly dilated a narrow strip of its anterior wall is resected and the canal closed with a fine continuous plain catgut stitch. It now remains only to fasten each strap to the buttonhole in the rectus sheath, with silk or nylon, and suture the two ends of the strap together as an additional security. The skin is closed.

The operation can be completed in 20 minutes. The catheter is left in situ for 48 hours. The patient is allowed out of bed the next day and can leave hospital as soon as the skin sutures have been removed.

I can only claim to have performed the operation 18 times. The theoretical soundness of the procedure, the uniformly good immediate results, the minimal disturbance to the patient and the short hospital stay, make it, I submit, worthy of trial. There should be little risk of perforating the vagina in passing the forceps to create the sub-urethral tunnel. In the remote chance of this occurring, the intra-vaginal finger would detect the error and an immediate closure of the vaginal mucosa could be effected. Retropubic space venous ooze can escape by dependent drainage between the interrupted fourchette sutures. Should undue elevation of the bladder neck be caused by the sling this could be remedied by the simple expedient of re-opening the small suprapubic skin incision, cutting the supporting nylon sutures and refixing the sling less tautly.

I would suggest that this operation would appear to fulfil the accepted canons of reconstructive surgery: (1) Restoration of function, (2) Re-establishment of normal anatomy. (A coloured film of this operation was then shown.)

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[1] MILLIN, T., and READ, C. D. (1948) *Post. Grad. med. J.*, **24**, 51.

Mr. H. H. Fouracre Barns: *Demonstration of film of round ligament sling operation for stress incontinence.*—The film shows a sling operation in which the round ligaments are used to make the sling. The sling passes beneath the bladder neck and approximates the bladder neck to the posterior aspect of the symphysis pubis and at the same time elevates the pelvic floor.

Mr. J. J. O'Sullivan (*from the Dept. of Gynæcology, St. Bartholomew's Hospital*): *Demonstration of film:* "Shaw's Sling Operation".—Our indications for this sling operation are patients who show a downward and backwards prolapse of the urethra and bladder neck and a patulous external meatus, and in whom true stress incontinence can be demonstrated in the examination room. Also all cases of stress incontinence following on previous vaginal operations.

We consider a new sling operation necessary because of the high recurrence rate following the use of other slings, in our hands, and also because of the serious post-operative complications and of the technical difficulties in achieving the desired result even though the operation is theoretically sound.

A broad band is necessary as the whole urethra needs support and, what is more important, because the localized pressure produced by a narrow band on such a weak structure as the urethra produces sloughing or stricture formation with their attendant dangers such as fistulæ and renal complications. If the narrow band is not placed in its correct position immediately under the internal urethral sphincter, it does not produce a physiological cure but only alleviates the symptoms by kinking the urethra under conditions of strain. It may also cause complete retention.

Fascia lata would appear to be the ideal source of this sling as, when it is taken from the lower end of the aponeurosis, it does not stretch and is stronger than other types of fascia. It also obviates the necessity for rather long abdominal incisions and the difficulties encountered in patients who have had previous abdominal operations.

It is absolutely essential to open the anterior vaginal wall so that the sling may be placed in its correct position and to avoid blind or semi-blind dissection which, again, is a potent source of urinary fistulæ.

We regard the direction of the sling to be so important that we drill holes in the pubic bone to achieve the desired result. The urethra in its normal position is at an acute angle

to the symphysis pubis and, to replace a prolapsed urethra in this position, the sling must go through the upper end of the pubic bone near the mid-line. Also the fibromuscular ligament which passes between the anterior loop of the internal urethral sphincter and the posterior surface of the symphysis pubis acts in this direction.

An obvious criticism of this operation is that it is liable to produce clinical shock. An anæsthetist is always a better judge of the degree of shock than the surgeon who is performing the operation. Our regular anæsthetist, Dr. Langton Hewer, says that the degree of shock produced during this operation is on a par with that produced during an average vaginal hysterectomy. A deep anæsthetic is necessary.

Excessive hæmorrhage is rarely encountered and then only when the para-urethral tissues are incised. It is impossible to stop this at its source but it always stops when the sling is placed in position. No patient in this series required a blood transfusion.

We have performed 75 of these operations and the follow-up period ranges from one month to two years. Comparing the results of these two operations, the following figures would appear to be of interest.

We have performed 17 obturator operations and in 3 of these failed to cure the stress incontinence, a recurrence rate of 17·6%. We used tantalum wire gauze instead of fascia lata in 4 of these cases. They were all relieved of their symptoms but ulceration of the anterior vaginal wall occurred in 3 of these. There was 1 death in this series, a patient dying in coma as a result of uncontrollable diabetes. We have abandoned the obturator operation because of the recurrence rate. 58 pubic-bone operations were performed with one failure; a recurrence rate of 1·7%. The following post-operative complications occurred: Urinary tract infections, 4 cases. Hæmatoma of vulva, 1 case; Phlebothrombosis, 1 case. There were no cases complicated by shock, hæmorrhage, osteomyelitis or urinary fistula.

Mr. Harland Rees: If the bladder is filled with dye and a film taken whilst the patient is straining down, descent as shown on the X-ray may be due to bladder-neck descent or to the presence of a cystocele or to a combination of both, and it is, therefore, difficult to gain precise information from this type of X-ray of the relevant fact in stress incontinence, namely bladder-neck descent.

At St. Peter's Hospital during the last year we have been using another method, first suggested by the Registrar, Mr. E. M. Nanson: A Foley catheter is passed into the bladder and the bulb is distended with dye, the catheter is then pulled down gently so that the bulb is in direct contact with the internal urinary meatus. A film is taken with the patient standing but at rest, and a second film is taken with the patient in a similar position but straining down. This gives a fairly accurate measure of the movement of the bladder neck.

Mr. Rees showed a number of slides to illustrate this method.

Mr. A. W. Badenoch: As it is exceptional to see stress incontinence in the nulliparous, the majority of the cases with whom I have had to deal are referred by gynæcological colleagues, and all have had at least one reparative operation on the vagina. I first employed the Aldridge operation and later did the Millin sling. The mechanical principle is the same in each of these procedures and it is only the approach which is different. I have always been apprehensive of the danger of producing injury to the bladder and the urethra, when burrowing between these and the scarred vaginal wall. I believe the Aldridge approach is safer, but in my hands neither it nor the Millin has been sufficiently successful for me to be comfortable in accepting the considerable risk which is associated with each of them. Stimulated by my colleague Harland Rees, I have been performing a cystopexy of the type advocated by Everard Williams. It is a simple operation; there is no danger of tearing the urethra or bladder, and it works—at least as frequently as a sling operation. I have had success in one case in which a Millin operation done by me had been a failure.

Mr. B. Rickford: The first case I treated by the Millin sling operation was cured in spite of the following complication: Severe extravasation of urine into the cave of Retzius necessitated reopening the wound. The slings which had been bathed in urine for two days were gangrenous and were therefore removed. The patient recovered and the suprapubic fistula healed after three months. The stress incontinence was cured and the patient is still symptom-free three years later.

I am wondering, in view of the removal of the sling, how important is the part played by sepsis and scarring in the cure of stress incontinence by the Millin sling procedure.

Mr. Hugh McLaren (Queen Elizabeth Hospital, Birmingham): In the University Unit at Birmingham we take the view that any form of sling operation is a very serious matter for the patient, and the operation is therefore performed only when it is obvious that nothing else will effect a cure.

L. A. Cruttenden and myself have undertaken only 12 Aldridge operations in the past two years, but from this experience I think we can fairly say that the operation is relatively straightforward; certainly it is much less complicated than the procedure outlined by Mr. Millin in this Discussion.

In an attempt to limit sling operations as far as possible, we have on two occasions set out to undertake a vaginal plastic repair, to find (as anticipated) that even the most careful dissection could not produce adequate amounts of vesico-vaginal fascia. Flaps were then cut and used as in the Aldridge operation. This method of vaginal exposure, cutting of flaps and subsequent return to the vagina, requires considerable staff-work in the theatre to limit the risk of sepsis.

Mr. J. V. O'Sullivan: I have performed 6 operations similar to that described by Wilfred Shaw. I gave up the operation because 3 cases developed severe shock and because of the danger of infection in the cancellous bone.

It is necessary to teach patients, following Millin's operation, to relax to pass urine rather than to strain in the usual way. Recently I had a husband who complained that my Millin's operation had prevented his wife wetting herself when up and about, but now she wet both of them in bed as she dropped off to sleep.

My only criticism of Millin's operation is that the fascial slings are sometimes too weak. Recently I have used one broad fascial graft, instead of two as recommended by Millin, with excellent success.

Mr. W. Hawksworth: Although the operations, as demonstrated by both Mr. Read and Mr. Millin, look extremely easy the younger members of the audience should not be misled into feeling that they could perform the operation without difficulty. Those who have tried to perform a Millin sling No. 1 operation know just how difficult it can be, and therefore it should be realized that all and sundry should not embark upon this new procedure without adequate training. I recently had the opportunity in New York of discussing this operation with Dr. Aldridge, and he stated himself that on occasions it was extremely difficult to find the plane of separation between the anterior vaginal wall and the urethra, and he had sometimes found it necessary to open the fundus of the bladder so that a finger could be passed down into the urethra in order to facilitate this dissection.

There is no doubt that where some form of sling operation is necessary, the Aldridge sling itself is easier to perform than the Millin sling No. 1.

Miss Doreen Daley: A patient of mine who had had a sling operation performed by Mr. Millin in 1948, had an easy vaginal delivery of a 6½ lb. baby three months ago. She had had no return of stress incontinence when seen at the post-natal clinic a few weeks ago.

Mr. Vivian H. Barnett: The Aldridge operation has been criticized on the grounds that it necessitates abdominal and vaginal approaches, which, not being performed together, lead to a prolonged operation. By using an abdomino-perineal extension to the operating-table, strips of abdominal fascia can be obtained by an assistant while the vaginal operation is performed.

I wish to ask Mr. Millin what the objection is to passing up the strip of fascia lata by the same route that the abdominal strips are brought down in the Aldridge operation, instead of making an incision anterior to the urethra as described in his "Millin's II Technique".

Section of Proctology

President—MICHAEL J. SMYTH, M.Ch.

[*January* 11, 1950]

Complications of Rectal Injections

By A. DICKSON WRIGHT, M.S., F.R.C.S.

THE injection treatment of hæmorrhoids which I believe was first evolved outside the medical profession has now secured a wide adoption within it. Providing an easy way out of a humiliating dilemma, it is much appreciated by the public and the profession also likes the method because it avoids an operation which even the most ingenious have found hard to make comfortable.

Like every other method it naturally has its complications and, as they are to a great extent avoidable, the preparation of this paper was thought to be worth while.

Allergic manifestations and pyrexia occasionally are encountered and this most probably was due to the oily medium rather than the 5% phenol. During the war when the medium was changed from almond to arachis oil, there were numerous complaints of dizziness and fever lasting for two or three days and occasionally the appearance of an urticarial rash. Almond oil seems to be free from these disadvantages.

Hepatic disturbances probably arise from intravenous injections with a condition of oil embolism of the liver resulting. I have had 2 cases of this, the patients being severely ill with epigastric pain and muscular guarding, a sharp pyrexia and even a rigor. In 1 case the victim was a medical man (a radiologist) and he was quite sure that he had perforated a long-standing duodenal ulcer. Radiological examination revealed no gaseous crescent and the condition got well in three days. In the other case the acute painful stage was followed by a transient jaundice and a swollen tender liver. The moving of the point of the needle during injection if the submucosal wheal does not rise should avoid this complication, which can be very alarming.

Necrosis and hæmorrhage seems to occur in cases where a second course of injections is being repeated after an interval. The previous scarring prevents even spreading of the oily fluid, so that excessive tension and blanching is produced and the mucosa undergoes necrosis. The ulcer produced being above the area of sensation, no pain is produced, but the patient notices the bloody discharge and the rectal irritability. To prevent this complication the second series of injections should be placed in the gaps between the standard pile positions and the wheal should not be completely blanched by too forceful injections. Massage of the affected area with the finger should be given after each injection is completed so as to spread the oily fluid.

The bleeding from necrosis is rarely severe nowadays, but it was serious in the old days when pure carbolic or the glycerin of carbolic was used and stories were current in past days of fatalities from this cause.

Thrombosis and prolapse of the pile mass may follow injection. This is generally the result of injecting too low in the anal canal so that the injected and later the inflamed area may prolapse. The condition produced is the well-known one which used to be described as strangulated piles and while at its height the patient is unable to think of getting out of bed.

This condition is prevented by injecting the root of the pile above where "the purple joins the pink" as it has been aptly put. Furthermore, when prolapse is a marked feature it is inadvisable to inject for fear of this complication and on general considerations as well.

A *gangrenous condition of the anal canal* occasionally occurs and I recollect one such case demonstrated by the late Mr. Simpson-Smith. Rectal symptoms sometimes occur in agranulocytosis and make the patient seek injection treatment and I felt that this was the underlying condition in this case. Severe diabetes is also a contra-indication to pile injections and old and debilitated subjects are best left alone for fear of this phagedænic condition.

Genito-urinary complications are extremely important and become the subject of litigation because they are undoubtedly the fault of the injector. They occur only in the male subject and when the anterior pile is the target of the injection.

The 10 c.c. of oil are deposited in whole or in part into the prostate, the urethral wall, or even the seminal vesicles and may lead to any of the following conditions : (1) Retention of urine. (2) Hæmaturia. (3) Oleouria. (4) Hæmatospermia. (5) Prostatic necrosis and abscess. (6) Stricture of prostatic or membranous urethra. (7) Abscess of the seminal vessels. (8) Epididymitis which not infrequently breaks down to form an abscess. (9) Testicular atrophy which may be bilateral. (10) Chronic cystitis. (11) Recurring pyelonephritis with its consequences. (12) Renal calculus as a result of chronic infection. (13) Urinary fistula in the perineum from drainage or rupture of a prostatic abscess.

Six cases of this group have been actually encountered.

Three had retention with hæmaturia; all of these recovered completely, but in two the urine became infected as a result of the catheterization. There was one case of stricture of the prostatic urethra and this patient developed bilateral epididymitis with suppuration and secondary atrophy of the testicles and chronic prostatic abscess (drained rectally) and bacilluria. This patient required periodic dilatations of the stricture and on one occasion when this was done outside the shade of the chemotherapeutic umbrella, fulminating pyelonephritis with a three-day suppression of urine resulted. He has recently died from a carcinomatous colon.

The fifth case was one of prostatic stricture with atrophy of one testicle, prostatic abscess and recurring pyelonephritis. This patient also has a urinary fistula in the perineum where the prostatic abscess ruptured.

The last case developed a renal calculus and chronic resistant bacilluria associated with prostatic abscess. This bacilluria case has resisted all attempts at cure although the renal stone has been removed.

These cases need never occur if a good view of the area of injection is obtained and the wheal is observed to rise steadily during the process of injection. For this purpose a slotted speculum such as Perrin's is the best. I believe the Kelly's speculum does not allow the wheal to develop as it should and it also prevents the anal landmarks from being seen so that the injections may be made too high. Needless to say the needle should not be pushed through any resistant tissue nor should the injection fluid be forced in against strong resistance and any complaint from the patient of penile pain or micturition desire should be a warning to stop and take bearings.

Should hæmaturia or retention occur immediately after injection, it would be a good practice to incise the tense swollen prostate through the rectum and allow the oil to escape the way it got in. I have never had the opportunity to do this as the cases which came my way were not seen until the complications were well established, two of the cases were not encountered till one year after the commencement of trouble. In one of these cases, however, the prostatic abscess was incised through the rectal mucosa with benefit.

Injections of proctocaine for anal fissure sometimes result in very extensive abscesses. It is probable that the fissure has already induced a small satellite abscess in these cases and the deposition of a quantity of oil in the vicinity results in a rapid extension of the sepsis.

It is wise before injecting these cases with oil to secure a novocain anæsthesia first and then to make a very full examination and bi-digital palpation of the perianal tissues. It is very hard to explain away this abscess to the patient, immediately after the injection for which possibly too much was promised. In a recent case I opened a most extensive ischio-rectal abscess eighteen days after a proctocaine injection for a fissure and this patient developed an endocarditis from a *Streptococcus fæcalis* for which no chemotherapy availed.

Proctocaine injections for pruritus ani may similarly cause abscesses and also necrosis of the skin with ulceration. There is a certain school which employs alcohol for these injections and they anticipate cutaneous gangrene in nearly every case.

Mr. W. B. Gabriel: At St. Mark's Hospital we seldom use anything but the 5% phenol in almond or arachis oil, and I agree with Mr. Dickson Wright that special care must be taken when dealing with the right anterior pile. Our teaching is that the best and safest proctoscope is a tubular proctoscope of the Kelly type and personally I only use the Perrin proctoscope for minor procedures such as excision of hypertrophied anal papillæ.

As regards oil-soluble anæsthetics I am sure that they should not be used for deep chronic fissures, especially when there is evidence of infection at the base, and even in the superficial fissures there is good reason to believe that equivalent relief can be given by use of surface anæsthetics such as 3% decicain or anethaine ointment rather than by deep injection of an oil-soluble anæsthetic solution with its potential risk. So far as injection therapy for pruritus ani is concerned I join issue with Mr. Dickson Wright when he says that this is a current and accepted method of treatment: I find that most cases of anal pruritus are amenable to local or general treatment, and whatever the cause may be the patients have to learn not to scratch. The responsibility for stopping the scratching habit must surely be with the patient, and I believe it is a mistake for injection therapy to be given since then the surgeon tends to take upon himself responsibility for cessation of itching and the patient underestimates the effort that is required on his part. I have not injected a case of anal pruritus now for several years.

Mr. E. T. C. Milligan: In the treatment of first and second degree hæmorrhoids we find that the injection treatment provides a safe remedy. At St. Mark's Hospital day after day and year after year in the large out-patient clinics injections are made by surgeons and their assistants and no complications are seen except, rarely, a small superficial ulcer on the mucosa giving a little bleeding but no inconvenience, and it soon heals.

Complications can be avoided if the right solution is put into the right place.

The solution is 5% phenol in almond oil in doses of 3 to 4 c.c. injected submucously into each of the three piles according to size. So safe is the injection that some venture to put as much as 10 c.c. into one large pile.

The glycerin solutions now discarded acted with intolerable uncertainty so that after injection patients sometimes had to be admitted with hæmorrhage from deep ulceration more serious than severe cases of secondary hæmorrhage after hæmorrhoidectomy. They needed local treatment together with blood transfusion. Pain, too, occurred sometimes exceeding post-operative pain.

With the decision to use only the 5% solution of phenol in almond oil, confidence in injection treatment returned, fear and uncertainty of subsequent dire complications were banished.

The place and site of injection.—The place of injection is in the submucosal space of the pile around the blood vessels. The mucosa is about 1 mm. thick so the needle should not go deeper.

A sharp stab with a lightly held and balanced needle and syringe will convey the impression through the hand that the needle has pierced the mucosa and reached the space under the mucosa. Here the needle can be freely moved with the mobile mucosa which could not be done if it had entered the muscle wall or extra-rectal tissues. The first few injected drops will balloon out the vascular mucosa and so further verify that the needle is in the right place.

The site of injection is the ano-rectal ring where the rectum ends and the anal canal begins; an easily observed locality for here a ring of mucosa first closes into the lumen of the tubular proctoscope like the shutter action in an iris diaphragm as the proctoscope is withdrawn from the distended cavity of the rectum into the anal canal. This site is the pedicle of the pile at its junction with the internal pile and further identified by the pink colour of the mucosa.

Solution injected at this locality will freely spread up into the pedicle and down into the internal hæmorrhoid as far as the intermuscular septum. This septum separates the insensitive part of the pile from the sensitive skin covering the external pile below.

Success and safety of injection depend on the knowledge of the surgical anatomy of the part and the recognition of the parts of the pile more than on the kind of instruments used.

The overlooking of co-existing lesions in rectum and colon is a serious matter.

In perianal injections of proctocaine necrosis of skin can only occur if injections are wrongly made into the skin or between the skin and the corrugator cutis ani muscle. Such a complication is not serious, the slough will soon separate and the wound will heal.

Should infection follow perianal or submucous injection, a very rare happening, it would happily be confined to the submucous and perianal spaces. The resulting abscess or fistula could easily be dealt with. Should the injections be wrongly put extra-rectally or into the ischio-rectal fossa, a serious abscess or fistula requiring extensive operations and much time in healing would result; so injections into the ischio-rectal space should be avoided.

It should, however, be stated that perianal and submucous infection and abscess are the rarest of complications; an arresting fact when one reflects on the bacterial population of the coverings through which the puncture is made.

Mr. S. O. Aylett: Following the third injection for hæmorrhoids, a colleague of mine developed acute pain in the region of the liver. Within ten minutes of the treatment the pain was severe and the patient had to retire to his bed.

Within twenty-four hours the liver had become enlarged to two fingerbreadths below the costal margin, and mild jaundice resulted. He was confined to his bed for ten days before the condition subsided.

The injection was in no way different from the hundreds performed in proctological practice. No blood was withdrawn into the syringe before injection with 5% phenol in oil, and the treated hæmorrhoids ballooned up in the usual fashion. In spite of this it seems certain that some of the phenol had entered a vein and had been carried to the liver via the inferior mesenteric vein.

Recovery from the complication has been complete.

Three Unusual Cases of Colitis Treated by Surgery

By E. C. B. Butler, F.R.C.S.

The term colitis or ulcerative colitis has often been applied to any inflammatory condition of the large bowel for which no definite cause could be found. The time has now come when the term ulcerative colitis should be reserved for those cases where the whole or distal part of the colon is involved by disease and where the ulcerated mucosa has been demonstrated at sigmoidoscopy.

Segmental areas of colitis or those infections attacking the proximal colon should, I suggest, be placed in a separate category since their prognosis differs from true ulcerative colitis; if surgical treatment is required an ileostomy is rarely needed and their response to less drastic methods is most encouraging. The following 3 cases were all diagnosed: "? ulcerative colitis" at one time or another; none of them ever showed the true sigmoidoscopic picture of ulcerative colitis.

Case 1.—Female aged 23.

History.—Twelve months' gradual onset of diarrhœa and colicky abdominal pain; she lost 2 st. in twelve months. For the last three months she had noted a lump in her abdomen.

8.6.47: She was admitted to the London Hospital with the provisional diagnosis of tuberculous peritonitis.

On examination.—A wasted girl with an irregular pyrexia up to 102° F. Stools showed no pathogenic organisms. There was a large tender swelling in the right iliac fossa. A barium follow-through meal showed a filling defect in the cæcum with spasm and loss of haustration in the proximal colon.

Operation.—18.6.47: Laparotomy. The terminal 6 in. of the ileum were thickened and œdematous to form a tube which was attached to the anterior abdominal wall; this was the lump which could be felt before operation. There were many enlarged glands in the mesentery. The cæcum, ascending and transverse colon were thickened and indurated, the remainder of the large bowel was normal.

The ileum was divided and the distal end embedded some 2 in. above the diseased portion. The proximal end of the ileum was anastomosed end to side into the pelvic colon. After operation a swinging temperature developed and an abscess became evident in the right iliac fossa. Aspiration showed 20 c.c. of pus; culture showed at various times *Staph. aureus*, anaerobic streptococci, and *B. coli*.

The abscess was treated by repeated aspiration and injection of, at first, penicillin and later 1/10 gramme of streptomycin daily for six days. At the end of this time only a little clear fluid was withdrawn and the patient's temperature was normal. She then made a quick recovery and regained her weight rapidly. Since leaving hospital she has attended the follow-up clinic every three months. She has no abnormal symptoms or signs and is able to do her work.

Comment.—This patient was probably a case of Crohn's disease of the terminal ileum which had spread into the proximal half of the large bowel. The rapid relief of symptoms following division of the ileum with anastomosis of the ileum to the pelvic colon was most striking and so far colectomy has not been required. The sterilization of the abdominal abscess by repeated injections of streptomycin was also instructive; open drainage was avoided and so was the risk of a persistent mucous fistula.

Case 2.—Woman aged 35.

History.—Eleven months' diarrhœa, intermittent pyrexia and loss of weight.

On examination.—A wasted, ill woman with an irregular pyrexia. There were no abnormal physical signs. A barium enema showed signs of inflammation of the proximal colon as far as the beginning of the pelvic colon. Sigmoidoscopy was normal to 20 cm.

In spite of general treatment and blood transfusions her condition became steadily worse.

Operation.—20.8.47: Laparotomy. Chronic inflammation of the whole of the large bowel from the cæcum to the commencement of the pelvic colon; there the disease stopped abruptly. The transition from the thick indurated bowel to normal pelvic colon was most striking. The small intestine was normal.

The pelvic colon was divided 2 in. distal to the disease and the proximal end was brought out as a mucous fistula. The distal end was embedded. The ileum was divided, the distal end was embedded and the proximal end anastomosed end to side into the normal pelvic colon.

The patient made a smooth and rapid recovery; her appetite returned and she rapidly gained weight.

Since her operation she has attended hospital every three months. Except for an irregular discharge of mucus from her fistula she has no complaints. A colectomy has not been required.

This patient evidently suffered from that form of colitis which has been well described (Crohn, B. B., Garlock, J. H., and Yarnis, H. (1947) *J. Amer. med Ass.*, **134**, 334). In their experience about 8% of colitis cases fall into this group. Diarrhœa and rectal bleeding are not prominent symptoms but constitutional reactions are often severe and a large number of these patients develop arthritis. If untreated the colitis tends to progress distally until the whole colon may become involved.

The object of surgical treatment is to isolate completely the diseased colon. Division of the colon distal to the disease is considered an essential step otherwise the infection might still creep down the bowel and could then not only invade the rectum but also the site of the anastomosis and thus invade the small gut.

If symptoms persist after the exclusion operation then a subtotal colectomy can be performed when the patient's general condition is better suited to a major operation.

Case 3.—Man aged 46.

History.—Since the age of 21 he had suffered from severe attacks of asthma. In 1940 he was treated as a case of ulcerative colitis. Since that date he had had recurrent attacks of rectal bleeding with some diarrhœa. Lately he had been worse and his Hb had fallen to 43%.

On examination.—4.2.48: A pale man with no abnormal signs save those of chronic bronchitis. Sigmoidoscopy showed no ulceration but the mucosa was œdematous. A barium enema was normal. He was discharged home.

29.9.48: He was readmitted with increasing anæmia. Bleeding time, clotting time and prothrombin estimations were normal.

Operation.—28.10.48: Laparotomy. The whole colon from cæcum to lower pelvic colon appeared hæmorrhagic; the coats were œdematous but there was no real induration. If rubbed, the surface of the bowel resembled that seen over an active peptic ulcer. The abdomen was closed.

18.12.48: After consultation with the patient an ileostomy was performed.

9.3.49: Removal of the left half of the colon. He recovered well and attended the follow-up clinic; he was readmitted because of persistent bleeding from his mucous fistula.

28.9.49: The remainder of the proximal large bowel was removed. The operation was difficult as the mesentery was loaded with fat and bleeding was excessive.

His recovery was prolonged by the following complications: intra-abdominal abscess, fæcal fistula and *B. coli* bacteriæmia from a thrombophlebitis. Fortunately he survived all these catastrophes and is now home. In the future it may be possible to close his ileostomy by anastomosing it to the stump of his pelvic colon.

Pathological report on the removed colon (Professor Dorothy Russell and Dr. W. W. Woods):
Macroscopical

Resection of lower part of colon 9.3.49 (S.D. 415/49)

The piece of colon is about 20 to 25 cm. long and 3·5 to 4·5 cm. in circumference after some hours in formaldehyde. The mucosa is normally folded and is injected by numerous minute red specks. This redness is now only moderate and in places slight. There are no erosions, ulcers or membranes. There is no obvious thickening of mucosa (0·15 cm. thick), submucosa (0·3 cm.) or muscle (0·25 cm.). Meso-colic glands are very small (largest 0·4 cm. diam.). Three pieces of colon were taken for section.

Resection of cæcum and remainder of colon 29.9.49 (S.D. 3841/49)

The gut is about 78 cm. long and varies in circumference from 7·5 cm. in ascending colon to 4 cm. in splenic flexure, after one hour in formaldehyde. The mucosa in cæcum, ascending colon and hepatic flexure is deep red, in transverse colon paler, but quite pronounced red, and in remainder pinkish-grey. In the cæcum there are a few purplish-red patches and some of them have a very thin, opaque, grey membrane on their surfaces; there are smaller similar areas in ascending colon. The submucosa is swollen (about 0·5 cm. thick) and gelatinous, suggesting œdema. The appendix has numerous red patches on its mucosa. Meso-colic glands must be very small because none were found in the abundant fat.

Pieces taken for sections were two from cæcum and one each from ascending, transverse, splenic flexure and descending colon.

Microscopical

The changes are almost the same throughout all the nine sections taken from different parts of the large intestine removed at the two operations. They indicate diffuse inflammation of an ordinary simple type affecting mucosa and inner part of submucosa.

In the lumina of a moderate number of mucosal glands there are small masses of neutrophil leucocytes (pus), and occasionally red blood corpuscles. There are neutrophil leucocytes between the surface epithelial cells, these leucocytes being on their migration to the lumen of the gut.

In many places the superficial epithelium is absent. Most of this is probably due to post-operative trauma during examination of the specimen. But there are a few minute areas where neutrophil leucocytes have poured through breaches in the epithelium and these areas are therefore probably pathological erosions. There are, however, no well-established ulcers such as one would have expected to be associated with the clinical hæmorrhage.

Very numerous plasma cells are packed closely in the mucosal stroma, obviously in greater number than in normal mucosa. Eosinophil leucocytes are moderately numerous, but are not more than are found in many simple inflammations.

Mucosal capillaries are congested. Red blood corpuscles lie free in many small areas of mucosa, mainly superficial, and in the cæcum there are a few larger superficial hæmorrhages at breaches in mucosa and muscularis mucosæ, with on their surfaces indefinite membrane of red corpuscles, leucocytes, epithelial cells and a little fibrin, but it is difficult to exclude operative trauma as the cause of these.

The blood vessels just outside the muscularis mucosæ are dilated in all sections, and in this plane there is moderate infiltration with plasma cells, lymphocytes and eosinophil leucocytes. Occasionally this infiltration is concentrated around the vessels, but there is neither hyaline degeneration nor necrosis of any vessel.

In a section of descending colon there are in the submucosa two minute groups of giant cells like those of tuberculosis, but these minute groups are not like tuberculous lesions because although they contain lymphocytes, there are hardly any epithelioid cells. There is one similar group in the submucosa of the transverse colon. But these are the only items by which this superficial cæco-colitis differs histologically from other examples of simple inflammation. For instance, the changes are similar to those in ordinary acute catarrhal appendicitis.

The muscularis is normal.

The inflammation of serosa in some sections is obviously the result of previous operations.

I have never encountered a similar case before and was unable to find a similar one in the hospital records. In my opinion this man may have suffered from an allergic manifestation in his colon allied to his asthma. On top of these allergic attacks he had gradually developed a simple colitis which in time might have developed into a true ulcerative colitis. Neither at operation nor in the specimen was there any evidence that he had ever suffered from an ulcerative lesion.

Comment.—The diagnosis of colonic disease is difficult despite the aid of radiography: the diagnosis of ulcerative colitis should never be made in the presence of a normal rectal mucosa.

If surgical treatment is required for any type of colonic infection then multiple stage procedures should be carried out whenever possible; they are far safer and it is quite likely that the second operation may never be required.

Mr. Guy Blackburn quoted a case of regional colitis in a lady of 72, with a very short history and no disease in the small gut. This was analogous to regional ileitis, and it was clear that a process similar to regional ileitis could occur in the large gut without any lesion in the ileum or jejunum. The absence of lymph-node involvement in the large bowel contrasted with the clinical picture of Crohn's disease.

Mr. John Hosford said that he had not had the same happy experience as some other surgeons in excluding a loop of bowel affected by Crohn's disease but had found it necessary to do a second operation to excise the entire lesion.

Film: Perineo-abdominal Excision of the Rectum.—W. B. GABRIEL, M.S., F.R.C.S.

Before showing this film, Mr. Gabriel mentioned a few points as guidance to those who might contemplate having a surgical film made.

(1) As the operation proceeds from stage to stage the various steps have to be indicated either by "cutting" or by "fading". The "cutting" method is, I think, more neat and gives a quick transition readily appreciated by those who are familiar with the technique of the operation which is being demonstrated: whereas the "fading" method gives a blurred image for a second or two and this gives a warning that another step is following. Perhaps the "fading" method has some advantages for those who are not familiar with the operation. In this film both these methods are shown, the "fading" method being evident particularly in the perineal stage.

(2) When a long focus lens is used as it was in parts of this film, especially in order to get a close-up view of the perineal dissection, it must be remembered that the field is quite a small one, probably not more than 12–15 inches in diameter. Time must therefore be given to the film operator to get his camera properly aligned and focused, and if the surgeon wishes to demonstrate any particular point he must be sure that he is within the restricted field that is being filmed.

(3) As regards the use of titles and sub-titles, I think in a silent film such as this if long descriptive sub-titles are used they rather tend to break the continuity and smooth flow of the film. I therefore decided in this film to cut the legends down to the bare minimum, namely a short sub-title before each of the three main stages of the operation (preliminary abdominal exploration, perineal dissection, abdominal mobilization and completion of colostomy), together with an indication of the time usually taken over each stage in a reasonably favourable case.

[The colour film was then shown]

Mr. Gabriel then continued:

The advantages of this method may now be indicated briefly.

The perineal dissection is done early in the operation by accurate dissection.

The pelvis is cleared from below upwards: this is a great advantage when a massive growth has to be mobilized, especially in men with a narrow pelvis.

The rectum and whole of the pelvic colon are removed up to the left iliac colostomy: this is of much importance when related polypi or multiple carcinomas are present.

There is no intraperitoneal division of the bowel.

A steep Trendelenburg tilt is not required and when the peritoneal stitch is begun from below, most cases need no more than 15 degrees tilt head down, or possibly up to 20 degrees

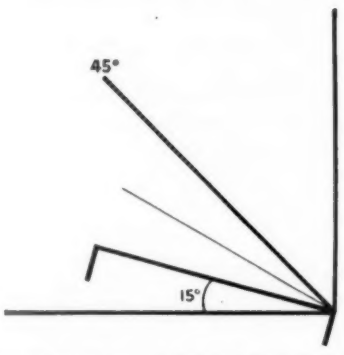


FIG. 1.—Diagram to show 15 degree Trendelenburg tilt, which is usually sufficient for a perineo-abdominal excision and even this is only required for a few minutes.

for a few minutes when closing the pelvic floor (Fig. 1). There is no doubt that a high Trendelenburg tilt imposes a great strain on the heart and respiration of many patients, especially

the short obese type, and predisposes towards post-operative pulmonary collapse. A maximum tilt of no more than 15 degrees is an ideal that can easily be achieved by the perineo-abdominal operation.

As regards anæsthesia, we seem so often to be called upon to deal with patients with extremes of blood pressure, both high and low, that I am now doing a series of perineo-abdominal excisions without spinal anæsthesia. A straight general anæsthetic of pentothal, nitrous oxide-oxygen, cyclopropane or ether is given and at the preliminary laparotomy I infiltrate the abdominal wall with 1% procaine (20 c.c. left and right) and also inject 10 c.c. of 1% procaine into the base of the pelvic mesocolon as the pelvic colon is held out by the assistant. Although under this regime a moderate drop in blood pressure occurs, the general condition of the patients has remained very satisfactory, with a slow pulse, and a very quick post-operative recovery to normal has taken place: of course the usual blood transfusion and glucose-saline drip has been given post-operatively but pressor substances have not been required.

The time taken by this operation is usually one hour and ten or fifteen minutes—less or more—according to the technical difficulties encountered.

The number of cases of carcinoma of the rectum and anal canal treated by this method, from 1932–1949 inclusive, has been 795 with a total mortality of 90=11·3%.

A fair indication of the reduced mortality since the adoption of stainless steel wire for the abdominal wall, with sulphonamide and penicillin therapy when required, is shown in the following table:

TABLE I.—PERINEO-ABDOMINAL EXCISION FOR CARCINOMA OF THE RECTUM AND ANAL CANAL (ONE STAGE)

Recent Operation Mortality

All hospital and nursing-home cases since August 1947.
Out of 151 cases, 7 deaths=4·6%

At St. Mark's Hospital:

1947	33 cases	2 deaths
1948	36 cases	1 death
1949	39 cases	1 death
Total	108 cases	4 deaths=3·7%

I wish in conclusion to express my thanks to Messrs. Kinocrat Film Unit for the time and trouble which they took in making this film.

Section of Experimental Medicine and Therapeutics

President—Professor G. W. PICKERING, M.A., M.B., F.R.C.P.

[*December* 13, 1949]

The German Food Shortage 1946–47 and Effects of Unlimited Food on Undernourished Men

By E. M. WIDDOWSON, D.Sc.

WHEN the Medical Research Council's Unit was established in Wuppertal in June 1946 the official rations provided 1,050 calories a day for the "normal consumer". Very few people lived as "normal consumers", however, because there were so many scales of supplementary rations that most persons managed to qualify for one or other of them. Extra food was also obtained in other ways, the most important of these being what was known as "Hamstering", that is, bartering goods with farmers in exchange for food.

The signs and symptoms of undernutrition in Germany in 1946 were those of a calorie deficiency, but not of the most severe type. The people looked pale, particularly the men, and most of them had lost a considerable amount of weight. The œdema was more common in men than in women, especially in men over 40, and it was usually confined to the legs. It generally disappeared after a few days' rest in bed. We saw no signs of vitamin deficiency, and there were no complaints of diarrhœa. There were, in fact, none of the signs of really severe undernutrition such as were found in the concentration camps.

Towards the end of 1946, an investigation was carried out on the effects of giving unlimited food for eight weeks to 19 undernourished men. Their ages ranged from 26 to 80 years. All but 2 had œdema and all but 1 were underweight. The extra foods they received were bread, potatoes and other vegetables, margarine, cheese, sugar, tinned meat and fish, and dried milk and cocoa. Their average calorie consumption over the whole period was about 6,000 a day, and their average gain in weight during the eight weeks was just over 10 kg. When the experiment ended and they went home, their body-weights fell again until June 1947, and thereafter there was a steady rise.

There was a significant rise in pulse-rate, basal oxygen consumption, serum and blood volume, hæmoglobin and hæmatocrit levels, and serum protein concentration as a result of the unrestricted diet. The blood pressures were low at the outset, and there was no rise during the course of the investigation. All the men suffered from nocturnal polyuria before the investigation began, and there was some improvement at the end of the experiment.

There was no change in the incidence or degree of œdema during the eight weeks of unlimited food, but it almost disappeared over the course of the next two years. The extracellular fluid volume was high at first, and there was a reduction in the absolute volume as well as in the volume expressed as a percentage of body-weight.

It is suggested that an increase in the volume of extracellular fluids is one of the most important changes brought about by undernutrition and that it takes place in all undernourished people, whether they have œdema or not.

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Serum Cholinesterases in Undernutrition

By R. A. McCANCE, F.R.S., M.D., F.R.C.P.

SINCE the general level of serum proteins was known to fall in undernutrition, and since the serum enzymes are probably specific proteins, we thought it might be interesting to estimate the activity of these enzymes in the serum of undernourished persons. No change was found in the activity of alkaline phosphatase which could be attributed to undernutrition, but serum cholinesterase was found to be low, and the activity rose as the plane of nutrition improved. It is thought that the level of cholinesterase activity in a person's serum is a reflection of his plane of nutrition, but the normal range is wide. Experiments in Germany showed that an improvement in diet gradually raised the level of cholinesterase activity to normal and that a return to insufficient rations led to a fall. The activity of this enzyme in the serum is not a reflection of the forced metabolism of any of the major dietary constituents, for 200 grammes of protein or fat per day for a week made practically no difference to the level of cholinesterase activity in the serum of undernourished persons. The pseudo-enzyme is more sensitive to the plane of nutrition than the specific enzyme, but both are affected. The activities of these enzymes in dogs or in male rats are not reduced by undernutrition but the activity does fall in the serum of female rats when they are starved.

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The Effect of Undernutrition on the Size of the Baby at Birth and on the Ability of the Mother to Lactate

By R. F. A. Dean, M.R.C.S., L.R.C.P.

The Unit of the Medical Research Council formerly working in Wuppertal made abstracts of the records of the local Landesfrauenklinik der Rheinprovinz for the years 1937 to 1948. The analysis of these data showed that, although there was no increase in the incidence of toxæmias of pregnancy, stillbirths or malformations,

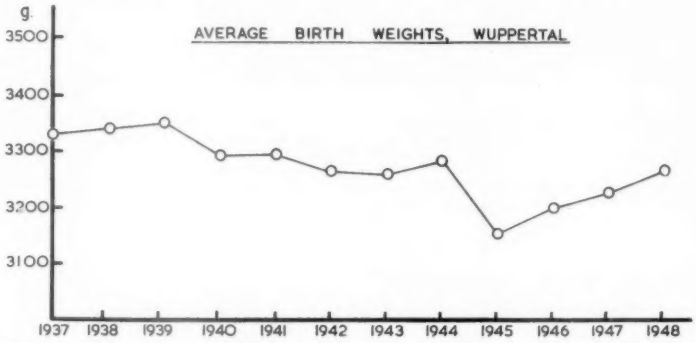


Fig. 1.—Average birth-weights of children born at the Landesfrauenklinik der Rheinprovinz, Wuppertal, 1937 to 1948.

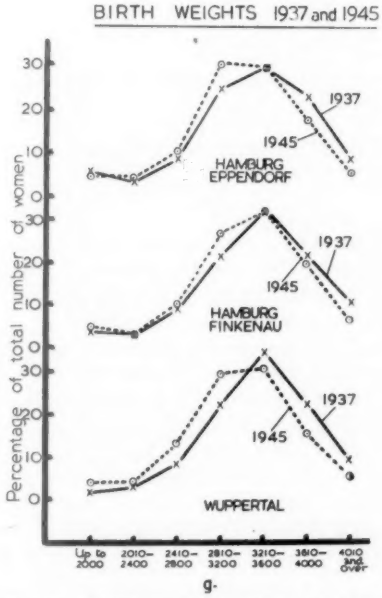


Fig. 2.—Percentage distribution of birth-weights in 1937 and 1945 at the Landesfrauenklinik, Wuppertal, and at two Hamburg hospitals. In each case the curve for 1945 is to the left of that for 1937 indicating that in 1945 more small children were born. The number of children involved in each analysis is between 1,200 and 2,600 and the differences are statistically significant.

there was a sharp fall in the average birth-weights in 1945 when the food situation was at its worst (Fig. 1). The children born then were about 185 grammes lighter than those born in 1937/8, but in the following years the weights rose again. The average length at birth was about 19 mm. less in 1945/6 than in 1937/8. The average period of gestation was shortened by 1·25 days but this would account for reductions of only 45 grammes in weight and 2 mm. in length in a normal child. Weight changes similar to those found in Wuppertal also occurred in Hamburg at the Eppendorfer Klinik and the Frauenklinik Finkenau (Fig. 2).

The ability of the Wuppertal women to breast-feed was greatly reduced in 1945/6 (Fig. 3) and the "physiological" loss of weight of the child after birth continued longer

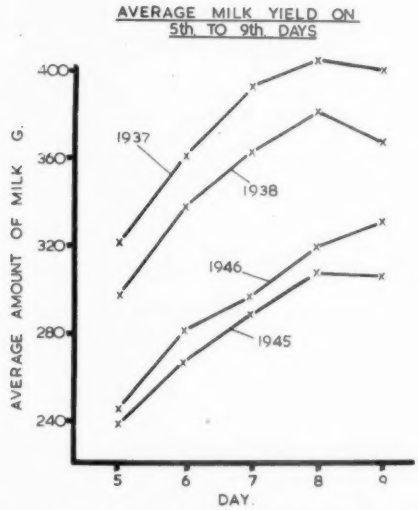


FIG. 3.—Average milk yields on the 5th to 9th days in 1937 and 1938, 1945 and 1946 at the Landesfrauenklinik, Wuppertal. The difference between 1937 and 1945 on the 5th day was nearly 90 grammes and there were similar differences on each of the other days.

than in 1937/8. The gain of weight in the first ten days was also slower, especially in the heavier weight groups. The progress of about 300 children born in 1946 was followed for the first six months and at the end of that time the average amount of weight gained was about 107% of the birth-weight.

The alterations in birth-weight confirmed the similar reports from the Hague, Rome, Stalingrad, Vienna and Erfurt and the fact that even a minor degree of under-nutrition such as that seen in Germany can reduce the size of the child appears now to be established. Lactation has not previously been studied quantitatively but there is no reason to suppose that the Wuppertal figures are unique. The causes of the failure of lactation are obscure. Some experimental work suggests that shortages of calcium in the diets may have played a part. It is also known that lactation is subject to psychological influences, and the mothers were probably adversely affected by the extraordinary difficulties that beset their daily lives.

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Section of Urology

President—Professor CHARLES WELLS

[*January* 26, 1950]

DISCUSSION ON ANOMALIES OF THE URETER IN CHILDHOOD

Mr. T. Twistington Higgins: The ureter, by and large, provides us with much of the amusement of children's urology and sets us many difficult problems in diagnosis and treatment.

Most of the anomalies which are met with are clearly vagaries of development: others are of doubtful ætiology, and some are certainly acquired.

CLINICAL PICTURE

The clinical picture is usually determined by urinary stasis, infection and deterioration of renal function though individual cases, for one reason or another, may present with other outstanding features, such as pain, hæmaturia or the presence of a lump or even calculi.

All too often the lesions are bilateral.

Clinical features.—(1) Infection—chronic or recurrent. Pyuria. (2) Disordered micturition. Excessive wetting in infancy. "Enuresis". (3) Pain. Often referred to the abdomen. (4) Lump. Hydronephrosis or abdominal cyst. (5) Defective renal function. Stunted growth. Sallow colour.

The normal ureter.—In the child, the *normal* ureter is outwardly identical in structure and function with the ureter of the adult.

Distinctive features in the child.—Yet there are distinctive features in the child's ureter which are of considerable practical importance. *Calibre*: In infants and very young children, the ureter is a tiny tube. In the newborn infant, a 4 F catheter is a full "fit". One can easily appreciate how readily inflammatory œdema can gum up the lumen and so determine persistence of an infection. In such circumstances, the passage of a catheter and distension of the pelvis with dye can be a valuable *therapeutic* as well as *diagnostic* procedure.

Neuromuscular reflex.—This reflex is notoriously sensitive in all the involuntary muscular tubes of the young (cf. pyloric stenosis, cardiospasm, etc.). The ureter is no exception. Spasm is readily induced and appears to be often very intractable. I feel sure this must be a significant factor in some long-standing infections. It *may* be the explanation of some cases of gross megalo-ureter and hydronephrosis. It is noteworthy that a common sequel to a cleared urinary infection is disordered micturition—urgency, frequency, etc.—"enuresis", if you like.

Symptoms of this kind may persist for months or even years, with a perfectly clear urine and no demonstrable structural abnormality. What may be called a "micturition stammer"—due, I believe, to delayed readjustment of this sensitive reflex.

"Neuromuscular reflex" is, of course, a high-sounding term which means little. Dr. M. Bodian has confirmed for me that the ureteral wall is well supplied with nerve fibres, but no ganglion cells. These appear to be massed in the vesical terminal.

EMBRYOLOGY

The main features are, of course, well established for us. The *ureter originates* as a bud from the lower end of the Wolffian duct of the 4–5 mm. stage, the two having at first a communal duct—the *common excretory duct*. This common duct later disappears leaving the two openings separate. With the development of the bladder, ureteric and Wolffian openings become more separated, so coming to occupy their normal positions:

(1) The ureter—trigone.

(2) Wolffian. *Male*—ejaculatory duct—floor of prostatic urethra. *Female*—The duct of Gartner in analogous position.

At the same time as all this is going on *below*, the bud is growing upwards with the metanephros, ultimately branching out to form the calyces and collecting tubules—which

finally link up with the secreting tubules of the kidney. All this is obviously a very intricate piece of development and it is scarcely surprising that it should sometimes miscarry. Such anomalies as reduplication and ectopic openings are sufficiently intelligible.

There is, however, very little precise knowledge about the fashioning of the ureteric tube, the evolution of its muscle, the finishing touches to upper and lower ends, and so on, and these are matters which are of great importance to us clinically. It may well be that the record of our observations may serve to fill in some of the gaps for the embryologist. We appreciate his difficulties. The fœtus he has to work with is even smaller than our babies!

Classification

Congenital.—Congenital anomalies of the ureter have been very completely classified by Meredith Campbell ("Pediatric Urology", 1937, I, 254, New York) and we may conveniently follow his main headings: (1) Anomalies of number. (2) Anomalies of origin and termination. (3) Anomalies of form, calibre and structure.

Anomalies of Number

Total absence of kidney and ureter.—We are only likely to see this in children when the solitary kidney goes wrong. I have met with it twice, for certain. Both these children were girls, of 10 and 12. Each had a huge infected hydronephrosis. The surprising thing was how long each survived with a mere shell of renal tissue—a matter of several years in each case. In neither of these children was there any sign of a second ureteric opening in the bladder.

Various rudimentary cystoscopic appearances are, however, described—dimples and hypoplasia of the trigone and even short blind stumps.

It is easy to be deceived into thinking one is dealing with a single kidney when œdematous cystitis makes identification of the ureteric orifices and retrograde pyelography temporarily impossible.

Reduplication.—This is a common anomaly. It may be *complete* or *incomplete—unilateral* or *bilateral.* And, since the fission virtually always proceeds from above downwards, splitting of the renal pelvis and kidney is associated. In the incomplete type, the ureters fuse at some point above the bladder, usually low down and even in the bladder wall. Our experience is that this incomplete type, with a single communal vesical orifice is the more dangerous. One ureter, more often that draining the lower renal unit, becomes blocked and, together with its associated renal segment, degenerates into a hopeless pus sac.

Where the ureteral fission is *complete* with two separate vesical openings, the prognosis seems to be better. Many of the infections we have seen in such cases have proved controllable, though, of course, not always.

Where two openings are present the lower always drains the upper pelvis, and the two ureters cross in their course. The accepted explanation of this is that the primary ureteric bud to the primary upper half of the metanephros retains its close relation with the Wolffian duct longer and therefore travels caudally with it, thus crossing the second ureter and assuming a lower site in the bladder.

Total extirpation. Dangers of stumps.—In the worst cases, the only satisfactory answer is uretero-nephrectomy—though hemi-uretero-nephrectomy may always be a possibility. Fortunately the renal pelvic segments are usually quite separate and arranged one above the other. They may, however, communicate (I have seen this occasionally) and they are said to be arranged side by side very rarely (I have not met this). These are eventualities which would make heminephrectomy impossible.

[Slides were shown to illustrate various types of reduplication and one of trifurcation.]

Anomalies of Origin and Termination

Ectopic ureter.—We have not seen many instances of this anomaly; I expect we have missed some. Diagnosis is difficult, especially in the male. The ectopic orifice is very commonly the opening of a *reduplicated* ureter, and being the *lower* of the two ureters, it therefore usually communicates with the *upper* renal segment.

The embryological association with the Wolffian duct explains the sites at which the ectopic orifice is most likely to be found; apart from occasional trigonal eccentricity these are: (1) In the male: (*a*) In the bladder wall. (*b*) Prostatic urethra. (*c*) Into the ejaculatory duct, or seminal vesicle. All these are *within the external sphincter.*

Incontinence is therefore not a feature though enuresis may be. Diagnosis is only likely when urinary infection is a complication, and it is therefore rarely made.

(2) In the female: The opening is most often found in the *vestibule* or the vagina, less often in the *urethra.* Incontinence is the rule and leads to diagnosis. It is noteworthy,

however, that in children, incontinence may be incomplete—at any rate, in the early stages. The child may be quite dry at night and when lying down and only wet when up and running about. And on occasion there may be no incontinence ar all.

Diagnosis calls for ingenuity. When the orifice is in the vestibule, there is little difficulty. When in the upper reaches of the vagina, careful observation may reveal a spurt of urine. Injection of indigo-carmine may help. Catheterization and retrograde pyelography are of course confirmatory. [Slides were shown.]

Suppression of the lower ureter with which may be associated a rudimentary renal segment may explain certain obscure retroperitoneal cysts presenting as abdominal or pelvic tumours.

Anomalies of Form, Calibre and Structure

This is the most important group of all, because it is by far the largest, including in fact most of the anomalies met with. Broadly it comprises:

(*a*) Megalo-ureter
(*b*) Hydronephrosis } With or without demonstrable obstruction.

One or two anomalies of form, not associated with dilatation, may be mentioned:

Ureteral aplasia.—By this is meant an underdeveloped ureter, associated with a hypoplastic or absent kidney. The ureteral lumen is small and there may only be a fibrous cord. Catheterization is impossible. A case was described.

Ureteral displacement.—This is rare in children, apart from tumours and obvious renal fusions. It is very rare in ordinary hydronephrosis (cf. adults). When present one expects something unusual.

Megalo-ureter.—"Hydro-ureter", all too often "Pyo-ureter".

I think we must attempt a clear distinction between *Primary* and *Secondary* megalo-ureter. I admit this is not always too easy. Obstruction at the bladder neck or in the urethra—*by reflux* gives us some of the handsomest of megalo-ureters.

But these are *secondary* lesions to which I can give only a passing reference, fascinating and important as they are.

I only wish to emphasize that in any case showing gross ureteral dilatation, especially if this is bilateral, the site of obstruction is most likely to be at the lower level. The *diagnosis of a lesion as being at the uretero-vesical level*, especially in a bilateral case, should only be accepted after the most careful exclusion of the infravesical possibilities.

I confine myself now to those lesions in which the ureter itself is—or at least appears to be—primarily at fault.

In a *primary* megalo-ureter, the search is, of course, for an obstructive lesion in the *uretero-vesical* region. Very often this is demonstrable, but equally often it is not. The fact is that for many of these megalo-ureters we have as yet no really satisfactory explanation.

The cystoscope may show us:

(1) A definite stricture seen as a small or even "pin-point" orifice. I think a pure mucosal stenosis is uncommon; usually the stricture is more extensive, involving at least the intravesical ureter, which means that effective dilatation will require more than a touch with the diathermy electrode.

(2) We may see the ureteric opening as a *large hole*, resembling the entrance to a *railway tunnel*. This is most often a *diverticulum* with a small true ureteral orifice somewhere in its depths. In lucky cases the catheter may find this and pass easily enough. It is just as likely to fail to do so. This is one of the more common anomalies and one feels it must have an embryological explanation. Chwalla offers important evidence on the point and I hope Mr. Williams will enlarge on it later (Chwalla, R. (1927) *Urol. cutan. Rev.*, **31**, 499). In these cases it would seem that there must be some associated local muscular defect, whether of structure or of tone, to account for the readiness with which reflux occurs.

In other cases, which are much more uncommon, the "railway tunnel" orifice is a *genuine patulous opening*, leading into an equally patulous ureter. Often spoken of as the "fœtal" type. Gérard, L. (Thèse, Paris, No. 63, 1908. "Le form de l'uretère chez le foetus et le nouveau-né") deduced from his researches that the "ureteral bud was wide and large up to the fifth month of fœtal life. (Quoted by Irvin, G. E., and Kraus, J. E. (1948) Congenital megalo-ureter and hydro-ureter, *Arch. Path.*, **45**, 752.)

(3) We may see a *ureterocele*. This is not a common finding in children. It may be that it is a later development. It is often associated with a duplication. It has been known to prolapse through the urethra in girls and a double one may completely fill the bladder. With luck, the ureteral orifice may be seen somewhere on the circumference. It must be considered an obstructive lesion and treated as such. I do not think that simple diathermy is enough. Excision with real dilatation has given us satisfactory results.

(4) *Lastly and perhaps most commonly of all.*

The ureteric opening looks perfectly normal, the catheter passes with ease, and there is, in fact, no obvious abnormality. In this type the lower ½ to 1 inch of the ureter above

the bladder also appears perfectly normal both macroscopically and microscopically. Yet there is a gross dilatation above.

What is the explanation of these cases? Are they congenital or acquired? The analogy to the Hirschsprung colon is remarkable. (Incidentally megalo-ureter is not commonly associated with Hirschsprung as is so often stated. In all our recto-sigmoidectomies, we have inspected the ureters carefully, and only once seen any sign of dilatation. It may of course develop later in life from prolonged pressure of the huge colon.)

Treatment

(1) *Conservative treatment.*—If stricture of the orifice has been definitely diagnosed then it must be dilated.

For a *pin-point mucosal stenosis*, diathermy will, of course, suffice, but, as I have said, this is rare.

True stricture, whether it be congenital or spasmodic, demands something more. Instrumental dilatation through a cystoscope has its very distinct limitations in childhood, and is, at present, only appropriate in selected cases.

To be certain of really efficient dilatation one must usually open either bladder or ureter or both and use bougies and so on. On the whole I think the *ureter* operations have served us best.

In that group with what one must call *achalasia* effective dilatation seems to be of some real value.

The analogy of this type to Hirschsprung's disorder of the rectosigmoid has, of course, suggested to us the possibility of a "pull through" operation. But this has not yet been attempted by us on a living subject. It may prove useful one day.

For the *ureterocele* we have excised the whole ureterocele, suturing the edges after bougie dilatation. The procedure seems to have worked well but I am sure the operation must be a radical one.

One or two other practical points. Where the ureter is tortuous and redundant, it is obvious that even if we relieve any obstruction below successfully, drainage may well be still deficient. Adhesions form between the loops, and stagnant pools persist. Ureters of this type must, I think, be straightened out and even shortened by excision of a segment.

I always fight shy of *reimplantation* myself, feeling that however "dud" the existing ureterovesical junction may be, it is probably better than any I should manage to make.

Finally a greatly dilated ureter should, I am sure, be drained to give it a reasonable chance to recover its tone.

(2) *Radical.*—When extirpation is done it should be *total*. Any sizeable ureteral stump may remain a source of infection and secondary removal can be a difficult operation.

Finally one must say a word about lesions at the *upper* end of the ureter.

Like megalo-ureter, hydronephrosis may be: *Primary* or *Secondary*.

Secondary hydronephrosis will eventually ensue from any ureteral dilatation provided it is sufficiently prolonged. In the young child, the pelvi-ureteric "sphincter" mechanism does "buffer" the kidney for some time surprisingly well. It is an ally to be made the most of.

Primary hydronephrosis is fortunately often unilateral and the determining causes—strictures, kinks and bands, whether or not associated with aberrant vessels, high insertion of ureter into pelvis or in rare cases, apparently "achalasia"—are all more easily understood because they can be exposed and inspected.

In the child we are perhaps more often fortunate to get on to hydronephrosis early, while there is still a kidney worth saving. (If only it were more generally recognized that a child's abdominal pain is not necessarily always in the abdomen!)

We have at any rate carried out conservative procedures of one sort or another in some 40 or 50 cases now, and the results are very gratifying.

Mr. R. K. Debenham showed lantern slides of three cases. The first case was a little girl aged 3 who presented with recurrent attacks of right-sided pyelitis. Excretion pyelography showed a double renal pelvis on the right side, with a double ureter which joined its fellow above the bladder. Cystoscopy showed a normal bladder and ureteric orifices. There was some hold-up in the excretion from the upper of the two right renal pelves, so a hemi-nephrectomy was performed with removal of the upper of the two pelves and most of the corresponding ureter. A subsequent pyelogram showed that the remaining half of the kidney was functioning well. For excretion pyelography in small children Dr. R. Astley, Radiologist at the Children's Hospital, Birmingham, was using hyalase mixed with 12% diodone, given subcutaneously into the buttock in a 30 c.c. dose and the results were most gratifying.

The second case was a girl aged 4½, who presented as a case of nocturnal enuresis but the mother's history was quite definite; she said "this child is always wet". Investigations

showed an ectopic ureter on the right side which opened into the urethra distal to the sphincter; the corresponding kidney was hydronephrotic. The left kidney and ureter were normal. Nephrectomy was performed and the child has been dry since.

The third case was that of a girl aged 10, who also presented as a case of enuresis but on careful questioning it was apparent that the child was always damp and the mother thought she "leaked" after passing water, though she micturated in the ordinary way. Intravenous pyelography showed that she had a double renal pelvis on the right side associated with a single ureter opening in the normal position in the bladder. On the left side, however, there was a double renal pelvis and a complete double ureter. The lower of the two pelves opened by a normal ureter into the bladder and cystoscopy showed no abnormality. The upper of the two renal pelves drained into a second ureter which opened into the urethra almost at the vulva. Owing to stenosis near the lower end of this aberrant ureter a retrograde pyelogram was impossible; there was hydro-ureter and hydronephrosis of the affected pelvis. A left heminephrectomy was performed and the child has been dry since.

Mr. R. A. Mogg showed films of a boy aged 9 who presented a rather unusual anomaly, namely a unilateral double ureter with one of the ureters opening ectopically at the bladder neck as a ureterocele. The boy had had a right-sided pyelocystitis since the age of 3 and had been investigated previously at various hospitals with inconclusive results. He was first seen by the speaker at the age of 6. Apart from the fact that he had had these recurrent attacks of pyelocystitis he was otherwise a normal child. An intravenous pyelogram showed an interesting state of affairs. There was a right renal outline, but there was no secretion from this side. On the left side there was a grossly dilated ureter, the dilatation being greater at the lower end, and there appeared to be a stricture of the lower end of the left ureter. It was difficult to obtain a true cystoscopic appearance of the bladder, but cystoscopy did show a large cyst-like structure occupying the whole of the trigone and preventing further examination of the rest of the bladder; it was then decided to explore the bladder. On opening the bladder it was seen that the whole of the trigone was occupied by a large submucous cyst-like structure which was in fact the dilated ectopic ureter of the right side which was opening as a ureterocele at the urethral orifice. The dilatation was so great that it was causing a definite obstruction of the left ureteric orifice and also of the normal right ureteric orifice. The ureterocele was resected and the trigonal mucosa was sutured and a new ureteric orifice was made below the existing one on the right side. The bladder was drained suprapubically. Convalescence was uneventful and since operation there have been no further attacks of pyelocystitis. Intravenous pyelogram now shows a poor secreting right kidney with a normal secreting left kidney, but the dilatation at the lower end of the ureter on that side still persists. Retrograde catheterization of the three ureteric orifices, namely, the left and the two right ureteric orifices, was quite easy. There was no evidence of any obstruction of an organic nature to any of these ureteric orifices. Specimens of urine have been obtained from the right ureteric orifices on three occasions and they have all been sterile on culture giving no evidence of any active infective process in the right kidney. The interesting thing in this case was that there were two conditions present, a complete double ureter on one side with one of the ureters opening ectopically at the bladder neck as a ureterocele and associated with what appeared to be a stricture or spasm of the ureter on the other side. It had been suggested that the so-called stricture on the left side might have been due to adhesions between the lower end of the ureter and the vas giving rise to the peculiar pyelographic changes. The fact that this ureter could be catheterized very easily would rule out the possibility of an intrinsic pathological process being responsible for the so-called stricture.

Mr. D. Innes Williams said it was to be regretted that in connexion with these cases of congenital megalo-ureter more was not known about the fœtal ureter. It was generally agreed among embryologists that by the fourth or fifth month of pregnancy the fœtal ureter was comparatively wide, straight, and of uniform calibre, but that after that dilatations and deformations occurred, with narrowing at the pelvi-ureteric junction, the pelvic brim and where the ureter passed through the bladder muscle. It was not clear why the dilatation appeared. Although the experimental evidence was rather confusing it did not seem very likely that the urinary secretion was adequate to "blow out" the ureter. Possibly the reason was that the ureter was at first growing more rapidly in comparison with the rest of the fœtus, and later in pregnancy it grew more slowly, and this was borne out by studies of pathological dilatations in dead fœtuses. If there was persistence of the fœtal ureter of this latter type there would be a hydro-ureter with an intramural part of normal calibre. In order to get the wide gaping orifice it seemed as if there must be some defect at a very much earlier stage, and a defect in the form of the bladder muscle, not of the ureter or ureteric muscle. Chwalla (1927, *Urol. cutan. Rev.*, **31**, 499) had described the formation of a membrane from the time that the ureter departed from the Wolffian duct, and had suggested that this membrane was responsible for ureterocele, and, moreover,

that its partial delay and eventual disappearance were responsible for congenital diverticula at the site of the orifice. He showed an illustration from an early paper indicating the urogenital sinus with the ureters opening into it, and the terminal dilatation of the ureter. This was at a very early stage when the musculature of the bladder had not yet formed. It had been suggested that if the membrane persisted for a little it might lead to the persistence of the terminal dilatations, which would then present, in post-natal life, as pouches at the site of the orifices. Several of these cases had, in fact, pouches into which the ureter opened, and in such cases the ureter above was very widely dilated indeed and allowed free reflux.

Mr. Innes Williams suggested that in these cases of megalo-ureter with gaping orifices this defect in the bladder muscle was the primary defect, and that the strong contractions of the inflamed bladder had, in the absence of the uretero-vesical valve, blown up the upper part of the ureter. Perhaps that was the only defect, though there might, of course, be some defect in the ureter also. It did suggest that if the ureter could be kept clean and sterile these cases would not progress and there would be no evidence of renal failure.

Mr. H. P. Winsbury-White said that there was one type of dilatation about which he wished to speak, and that was the mild dilatation which so often presented a practical problem in hospital and elsewhere. This was seen, of course, in cases of infection, and the academic point arose as to which came first, the dilatation or the infection. It was known that dilatation was a constant accompaniment of infection in a mild degree. The problem could not be solved on the spur of the moment. The infection was dealt with for the time being by medication, but it tended to recur as intermittent pyelitis and cystitis. The bladder should be investigated to make certain whether there was or was not any residual urine there. The dilatation of the ureter might be expected to continue, if the residual urine in the bladder could not be made to disappear.

There was another point about the dilated ureter. As far as stone in the upper urinary tract in children was concerned dilatation was a most important ætiological factor. Many of the cases discussed that evening also had residual urine in the bladder, and that added to the difficulty of treatment. He had occasionally brought about a temporary improvement in the child's condition by doing a suprapubic cystotomy, and in other cases he had resected the bladder neck. This was not an easy thing to do in a child. The approach to the internal urinary meatus through the bladder was very narrow and he had never succeeded where there was a large amount of residual urine in getting rid of such urine completely, although it had been possible to reduce it considerably.

Mr. David Band showed a number of lantern slides and discussed the differentiation of megalo-ureter due to uretero-vesical achalasia, from hydro-ureter associated with achalasia of the bladder neck. In the former the bladder emptied properly, and, there being no demonstrable stricture of the urethra or bladder neck, it must be assumed that there was a failure to relax at the uretero-vesical meatus. The pathology of achalasia was not understood, and he thought they should beware of adopting a rationalistic outlook which was the privilege of physicians and surgeons up to two hundred years ago, but which was a danger to those who practised medicine and surgery to-day.

He proceeded to show a number of urograms of cases of achalasia of the bladder neck. The first was from a young man who had reported for medical examination for the army. It was found that he had albuminuria. There was incomplete emptying of the bladder and the cystogram showed a grossly distended bladder with reflux up grossly dilated ureters. The blood urea was over 100 mg.%. At this stage he did a presacral neurectomy, and drained the bladder suprapubically. Eighteen months later the blood urea still remained as high as 80 mg.%, but the patient was remarkably well. A transurethral resection of the bladder neck was performed, and subsequently micturition returned to normal, and voiding was complete. The blood urea had since then fallen to 30 mg.%, but there was still regurgitation to the upper urinary tract. The patient was now in full employment as a miner.

The second case was that of a young soldier who also was found to have albuminuria. He had an over-distended bladder, but without regurgitation, as shown in a cystogram. There was again no apparent contracture of the bladder neck. After transurethral resection complete emptying of the bladder was restored. Microscopic examination of the resected bladder muscle revealed no abnormality of the muscle fibres or stroma, and no nervous elements.

The third example was a case of achalasia of the bladder neck in a little girl, and here again restoration of complete evacuation of the bladder contents and improvement of renal function was brought about by resection of the bladder neck.

In a series of cases of megalo-ureter due to achalasia presacral neurectomy had been carried out without any appreciable alteration in size for several years. Yet in the case

of a girl of 18 years who had severe infection of the right kidney and gross megalo-ureter on the right side, there was on the left side a lesser degree of achalasia with a typical "snake's head" ureter. A right nephro-ureterectomy was carried out and later the lower end of the left ureter was excised and a reimplantation of the ureter to the bladder was done. This girl two years after the reimplantation had remained well. A pyelogram of the result of the reimplantation showed that the ureter remained of normal size and the renal function was excellent, as demonstrated by intravenous pyelography and the ordinary function tests.

A boy at the age of 10 years, had infection of the urinary tract and was found to have a megalo-ureter of lesser extent on the right side and a gross megalo-ureter on the left. Presacral neurectomy was carried out, and function remained good seven years later, but without appreciable alteration in the size of the ureters. A similar case was one of bilateral megalo-ureter subjected to neurectomy with the same result. The last case was that of a boy aged 1 year in whom the cystogram showed an obstruction in the posterior urethra with gross dilatation of the ureters, and who had a congenital obstruction in the prostatic urethra. The case had been seen by Mr. Twistington Higgins, who had dealt successfully with the obstruction. Subsequently, Mr. Mason Brown resected the lower 4 inches of the ureter and carried out a reimplantation of the ureter to the bladder. He was glad to say that at the age of 3 years this boy was still very well. His baby brother, however, at the age of 4 months became very ill. There was a distended bladder. The ureters showed a marked degree of dilatation, and retrograde pyelography revealed a bilateral hydronephrosis. Symptoms of uræmia developed and bilateral nephrostomy was done. This was an extraordinary example of two brothers with exactly the same congenital malformation.

Mr. Band added that he could not believe that sympathectomy was necessarily the treatment of choice in cases of achalasia. If the urine was kept sterile very possibly the upper urinary tract would remain remarkably well without surgical intervention. In those cases in which a satisfactory renal function gave some expectation of reasonable chances of survival, excision of the recalcitrant segment of muscle offered possibilities. In megalo-ureter resection of the lower segment of the ureter and neo-uretero-cystotomy had given satisfactory results, and he was convinced that resection of the bladder neck was the treatment of choice in cases of urethro-vesical achalasia.

Mr. E. W. Riches said that he was stimulated to intervene in the discussion owing to Mr. Band's reference to sympathectomy. He himself was not a protagonist for sympathectomy. He agreed that until they knew more about the ætiology of megalo-ureter they did not know how to treat it. Apart from Mr. Williams' most valuable contribution, they had not heard much in that discussion about ætiology. They had seen Mr. Higgins's enormous collection and realized how difficult the problem could be for those who had regularly to treat children with these conditions.

He believed that the first case of sympathectomy for this condition was done in 1933 by Ogier Ward. That was a success, but later cases had not been so successful. He was sure that with such dilated ureters as they had seen that evening they would never have a complete success from sympathectomy because there was too much fibrosis in the ureter to allow it to resume its normal size.

He had had referred to him by Professor Alan Moncrieff a girl aged 4 who had recurrent *B. coli* infection. She had been treated for more than a year by medical means including sulphonamides, but always relapsed. Pyelography showed that there was a certain amount of dilatation of the ureters though never very gross. Having read Ogier Ward's paper, he carried out a pre-sacral sympathectomy on that child. From the picture five years later the ureters appeared normal, but the striking thing was that she ceased completely from that day to have her recurrent attacks of infection, and he was sure that in this case pre-sacral sympathectomy did good. She had a little sister born subsequently to her own operation, who had exactly the same history of recurrent attacks of *B. coli* infection. The condition in this second case was more marked on the right side than on the left, but both ureters were dilated. They waited until the child reached the age of 4, and then did a pre-sacral sympathectomy. The result as seen two years later showed that the regression had not been as marked as in the case of her sister, but the lower ureter was less dilated, and infective attacks had ceased. When the ureter was very large it was quite obvious that nothing like presacral sympathectomy was going to do any good, and he had not hesitated to reimplant the ureter into the bladder. The intravenous pyelogram showed a diminution of size after operation.

He felt, as he had already said, that they did not know much about the ætiology in these cases, but if they had only one case of this sort which did respond to sympathectomy they must seriously consider a neurological source of the dysfunction as the initiating cause, at any rate in some cases. But where there was a gross obstruction it must be relieved, and the bladder neck could be resected in some cases. It was in those cases in which no obstruction at all could be found that the difficulty arose. He hoped that if others got these cases at an early stage they would not feel that presacral sympathectomy was entirely to be avoided.

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The President reported the case of a child, first seen in 1928, with bilateral megalo-ureter. There was intense cystitis which was treated by the best means at their disposal in those days. He showed a slide illustrating the cystoscopic findings at the lower end of the ureter at the end of treatment. Here there was a sheet of mucous membrane which bore some resemblance to a ureterocele except that the central opening was large. A photograph showed the patient by the side of a normal youngster of the same age, revealing that the child was an excellent example of renal dwarfism. He thought that the retardation of growth was probable in these cases, and was rather surprised that none of the earlier speakers had mentioned it. He lost sight of the boy until 1943, when, a grown man, he turned up in good health except for a complaint of persistent pain on the right side. The right kidney and ureter proved to be diseased and were removed. The left kidney and ureter were then quite healthy, although twenty years previously they had shown characteristic dilatation throughout. It appeared, therefore, in 1928, the importance of the disease was grossly exaggerated by superimposed infection and it appeared further that control of the infection had led to a degree of improvement which no one would have anticipated.

Mr. Twistington Higgins, in replying to the discussion, said that several interesting questions had been raised, notably in regard to the ureteral dilatations without obvious obstruction as seen in infants and less often in older children. Further work on the ætiology of these was essential. He stressed the adaptability of growth and the wisdom of non-interference, as far as possible, in infancy. He thanked Mr. Winsbury-White for calling attention to the minor cases of dilatation, and agreed that these were very troublesome and the infection persistent. This type probably fell into the group of spasm, undue irritability of the neuromuscular mechanism about which so little is really known. It was a type which could be controlled more readily with modern drugs. A better understanding of the neuro-muscular mechanism might well solve many problems in childhood, apart from those in the urinary tract.

It was perfectly true that the stone was commonly only an incident in an obstructive lesion, and the underlying cause must be dealt with. Removal of the stone alone was not enough.

On the question of residual urine, they had learned that many perfectly normal children had a certain amount of residual urine, up to quite an appreciable quantity (2–2½ oz.).

Resection of the bladder neck had been done in a number of his cases after careful selection, with considerable benefit. Children, otherwise unable to empty the bladder, had been able to acquire the facility of normal expression.

Sympathectomy had been mentioned by Mr. Band and Mr. Riches. He was not impressed by the results of either spinal anæsthesia or sympathectomy. He felt that more satisfactory help was available now in the form of drugs like pituitrin and more simple measures.

Mr. Twistington Higgins then thanked his colleagues at the hospital, its nursing staff whose patience and skill with these children was beyond praise, his devoted young assistants, who were such a valuable stimulus, and Mr. Derek Martin for invaluable help with the illustrations.

[*November* 24, 1949]

The following cases and specimens were shown:

Bilateral Calcareous Tuberculous Kidneys.—Mr. G. E. NELIGAN.

Metastatic Staphylococcal Infection of Kidney.—Professor VICTOR W. DIX.

Invasion of Kidney by Metastases from Carcinoma of Rete Testis.—Mr. G. M. LUNN (introduced by Mr. A. W. BADENOCH).

Renal Carcinoma with a Secondary Deposit in the Vulva.—Mr. C. G. SCORER (introduced by Mr. H. G. HANLEY).

Transplantation of Right Ureter into Colon for Old Tuberculous Cystitis with Complete Incontinence (Previous Left Nephrectomy for Tuberculosis).—Mr. A. CAVENDISH.

Carcinoma of Ureter.—Mr. J. GABE.

Four Specimens of Vesical Diverticulum with Growth.—Mr. R. B. WELBOURN (introduced by Professor CHARLES WELLS).

Pedunculated Carcino-Sarcoma Arising in a Diverticulum with Intermittent Prolapse into Bladder Cavity.—Mr. D. M. WALLACE (introduced by Mr. JAMES CARVER).

Recurrent Prostatic Adenoma with Bladder Stone.—Mr. A. E. ROCHE.

? Granuloma of Prostate (for Diagnosis).—Mr. J. G. YATES BELL.

Section of Otology

President—GAVIN YOUNG, M.C., M.B., F.R.F.P.S.Glas.

[*December* 2, 1949]

DISCUSSION ON THE MEDICAL TREATMENT OF AURAL VERTIGO

The Medical Treatment of Ménière's Disease

By J. KODICEK, L. R. S. TAYLOR and G. H. BATEMAN

(*St. Thomas's Hospital, London*)

Mr. G. H. Bateman: The work on which this contribution is based has been done at St. Thomas's Hospital and Mr. L. R. S. Taylor and Mr. J. Kodicek have been largely responsible for it. Mr. Taylor will give details of the cases treated and the results obtained in our series.

There are two conceptions of Ménière's disease, firstly that it is a primary affection of the vestibular apparatus and, secondly, that it is a vestibular manifestation of a constitutional disorder. We think that most would agree that the second hypothesis is correct and this opinion is supported by the various medical treatments that have been discussed and tried in the past few years, e.g. Mygind and Dederding's restriction of fluid intake and salt-free diet, treatment with urea to aid excretion of sodium, and also by Wright's focal sepsis and the Scandinavian intestinal intoxication theories. Incidentally we may be wrong in ascribing this latter to Scandinavia as it has been the basis of the spa treatment of Ménière's disease, and other diseases, for a long time. Histamine therapy is based on a vasoconstriction theory of the causation of the disease and it appears that Miles Atkinson's theory grew out of this. It is very difficult to trace the origin of the various theories as they soon get distorted. Miles Atkinson's latest paper read at the Fourth International Congress in London in July 1949 emphasizes vitamins, and histamine is mentioned only as a convenient method of differentiating between the various vitamin-B deficiencies.

Results of treatment are very diverse, but the varied habits of living and perhaps climate of many countries may provide different causes of labyrinthine pathology, and therefore the results of treatment found in one country cannot always be comparable with those in another.

On analysing the results of the treatment we have followed at St. Thomas's Hospital we feel that, while not curing all patients of their symptoms, we have succeeded in providing them with a *modus vivendi*, free from the fear of sudden crippling attacks of giddiness.

This treatment is our interpretation of one advocated by Miles Atkinson in 1946 in a paper read to this Section at Torquay (*Proc. R. Soc. Med.*, **39**, 807). His theory was that the vertigo is caused by a vascular disorder of the small vessels of the labyrinth resulting in excessive formation of endolymph. This disorder may be primary vasodilatation with excessive transudation supposedly through the stria vascularis of the scala media, or a primary vasoconstriction of the arterioles which leads to an anoxia of the capillaries and this in turn leads to excessive transudation through the capillaries when the vasoconstriction passes off. This may be likened to Raynaud's disease. The two groups may be distinguished by a histamine skin test. 0·05 c.c. of a 1 : 10,000 solution of histamine (0·275 mg. of histamine diphosphate in 1 c.c.) is injected intradermally in the flexor aspect of the forearm 2 in. below the bend of the elbow. The result is read fifteen minutes after the injection. A negative reaction is a central circular wheal of about ¼ to ½ in. in diameter surrounded by an areola of 1½ to 2 in. in diameter. A positive reaction gives an irregular central wheal of 1 to 1½ in. in diameter with centripetal pseudopodia and a bigger areola round it of 2 to 3 in. in diameter. There are some intermediate results which should be retested with a double dose of histamine and those which are not definitely positive should be considered negative. There are difficulties in interpretation of this test and errors of classification become obvious in failure of response to treatment. When wrongly classified cases are often made worse by therapy and improved when the other treatment is substituted.

Negative cases are treated by vasodilatation; this controls the vasoconstriction and so prevents the anoxia which causes the increased permeability of the capillaries. Nicotinic acid is the vasodilator we have used and big doses must be given. 100 mg. t.i.d. is a moderate dose and doses up to 250 mg. t.i.d. have been necessary to relieve the symptoms in some cases. Intramuscular injections of 35 or 50 mg. of nicotinic acid are sometimes needed in the early stages. If the symptoms are controlled, dosage must be continued indefinitely though it can often be reduced.

Positive cases are treated by histamine desensitization. 0·05 c.c. of a 1 : 10,000 solution of histamine is first injected subcutaneously and the treatment is continued by repeating the injections on alternate days, increasing the dose by one-half on each occasion. The dose is taken up to about 0·4 c.c. of a 1 : 1,000 solution. It is rarely possible to take up the dosage at this rate throughout the course and if the reaction, flushing, palpitation and headache, is severe, the previous dose should be repeated and the rate of increase reduced. A course thus lasts about four weeks.

Miles Atkinson now advocates the use of enormous doses of riboflavin for positive cases, such as 90 mg. t.i.d. but the price is prohibitive in this country.

Mr. L. R. S. Taylor: Cases have been selected which fulfil the criteria laid down as constituting Ménière's disease: perceptive deafness, tinnitus and vertigo occurring in bouts. Headache or head pains have been found in nearly every case, and these have often been previously diagnosed as migrainous and have been centred on the ear.

Caloric reactions were tested after the method of Cawthorne, Fitzgerald and Hallpike, using water at 44° C. and 30° C., delivered for 40 seconds from a suspended douche can. Time was taken from the start of stimulation until nystagmus ceased as estimated by the observer using reflected light, and confirmed where possible by the patient. Fifteen minutes were allowed between each test, the whole test taking over an hour to complete.

Cases were divided into positives and negatives by an intradermal skin test made by injection of histamine two inches below the bend of the elbow in the centre of the flexor aspect of the forearm. The reason for this choice of injection site is to facilitate readings in doubtful cases and to aid in standardization. The grouping is dependent on the anatomy of the lymphatic system and therefore, for comparison, the same site must be chosen in each patient. Results are read fifteen minutes after injection. Straightforward cases have already been described. The doubtful cases show small serrations or even centrifugal pseudopodia, but these must be ignored. Any pseudopodium extending upwards, if associated with a good erythema and bleb, should be read as positive. If the injection is made subcutaneously the result will always be negative, hence the necessity for accurate placing of the needle.

Unfortunately the easiest way of learning to read these tests is the hard way of experience, which may be uncomfortable to the patient and disheartening to the physician. The results obtained have, however, justified the time spent.

The treatment of the negative group will be considered first. The patient is told to take 100 mg. of nicotinic acid three times a day before meals, and to expect a warm flush in the face, neck and forearms ten minutes later, lasting for about ten minutes. If no flushing occurs the patient is told to chew up the tablets before swallowing.

After a week the patient is seen again and, if nothing untoward has occurred, 100 mg. t.d.s. a.c., are given for a month before he is seen again. In severe cases intramuscular injections of 50 mg. or 100 mg. once or twice weekly, or even daily at first, have been given. A few cases were bedridden when first seen. These were admitted to hospital and treated with larger doses; injections of 75 mg. intramuscularly were given to one man three times a week at first. It is exceedingly important to stress the necessity of the continuation of a small maintenance dose when the symptoms are controlled. This will vary from patient to patient, but we have found 100 mg. t.d.s. to be an adequate dosage, although individuals often require a greater amount. This is a continuous treatment and makes no pretence of curing the underlying cause of the disease. The natural history is one of irregular bouts of attacks. These must still be expected by the physician and patient and, at the first warning sign, for example increase in tinnitus, an intramuscular dose is given of 50 to 100 mg. and an extra 100 mg. daily should be taken by mouth for a few days. In women, we have found an intramuscular injection of 50 mg. forty-eight hours before the expected menstrual period to be very effective in warding off an attack. Thorne and his co-workers have shown that in women there is a considerable sodium retention in the immediate premenstrual period with consequent cerebral œdema. Any tendency towards labyrinthine hydrops will therefore be accentuated at this time. The onset of acute coryza is another indication for increasing the dosage temporarily.

The histamine positives present a simpler group clinically for treatment, though in our hands results have not been so satisfactory as for the negatives. This is contrary to Atkinson's experience. Cases after completion of histamine desensitization have remained well for varying periods up to eighteen months, but all have required a second course, and it would seem that a maintenance dosage fortnightly or monthly is necessary.

The dangers associated with this form of therapy are few. Excess nicotinic acid is said to cause imbalance in vitamin B complex absorption. Two cases on very high daily dosage (800 to 1,000 mg. daily) have indeed shown such symptoms (emotional instability, feeling of fullness of head and photophobia) and both have been relieved of their complaints within a week by reducing their doses. A third case exhibited nausea, vomiting and water brash signifying a severe gastritis and a fourth constant diarrhœa, until the nicotinic acid was rested on the former, and dose reduced in the latter. These symptoms should be controlled by giving a compound vitamin B capsule.

Subcutaneous injection of histamine if given slowly will be without reaction, but if given too deeply into the muscles, or intravenously, produces alarming temporary symptoms of histamine shock (correctable by adrenaline (1 : 1,000 solution) minims v. intramuscularly, or intravenously) and in elderly hypertensives would not be without danger.

A total of 53 patients has been treated by the Miles Atkinson method. In none of these was there any doubt as to the diagnosis. All the patients attended a special clinic and were supervised by the same team of clinicians throughout. Caloric vestibular reactions have been studied in 37. The remaining 16 cases had no caloric tests for various reasons.

Age and sex distribution.—Of the 53 patients 23 were men and 30 women. The ages varied between 21 and 75, but practically half the patients were between 40 and 60 years of age.

TABLE I.—AGE AND SEX DISTRIBUTION (53 PATIENTS)

Age in years	20–29	30–39	40–49	50–59	60–69	70–79
Male ..	—	8	4	6	5	—
Female ..	1	4	7	9	7	2

Histamine skin reaction.—15 patients were "positive" (28%). This figure is rather higher than Atkinson's. 11 of these were females and 4 males. No special age incidence was noticed. The remaining 38 patients were histamine "negative" (72%) and both sexes were equally represented.

A number of errors in the histamine grouping were made early in the series, mainly through incorrect reading of the reaction and through subcutaneous injection of histamine. A marked increase in the severity of symptoms was noted in these cases, sometimes with remarkable suddenness. Repetition of the test and the institution of appropriate treatment resulted in rapid improvement and none showed any permanent ill-effects (e.g. increased deafness).

Effect of treatment.—Vertigo responded extremely well, being relieved in 32 (60%) cases and improved in another 20 (38%).

Tinnitus.—Relief was obtained in 12 (23%) and improvement in another 22 (42%). In the latter group the musical component was usually lost, leaving the pulsatile (vascular) tinnitus.

Deafness.—Both subjective and objective improvement in hearing was noted in 10 cases (19 %), the average gain in the speech range being about 10 decibels.

Headaches were noted as a marked feature in 25 cases (47%). Relief was obtained in 17 of these and improvement in duration and severity in a further 6 cases.

TABLE II.—RESULTS OF TREATMENT

	Vertigo	Tinnitus	Deafness	Headache
Relieved ..	32	12	—	17
Improved ..	20	22	10	6
No change ..	1	19	43	2

The cases have been followed up for a period of 18-30 months. The number of favourable results far exceeded that resulting from any other non-operative treatment we have tried. Furthermore the inconveniences to the patients of special dieting and restriction of water intake are avoided, while at the same time they are allowed to return to an active and useful life.

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——, HAROP, G. A., and ENGEL, L. (1940) in Recent Advances in Endocrinology, by Cameron, A. T. London, p. 215.

Mr. I. A. M. Macleod, *General Hospital, Nottingham.*—In June 1946 there was a group of 7 patients attending the Aural Department of the General Hospital, Nottingham, suffering from such severe symptoms of Ménière's disease that they were completely incapacitated. They had undergone practically all the recognized courses of medical treatment, and in three instances surgical measures had also been carried out. Unable to work, their symptoms unrelieved, they had abandoned all hope of being able to live useful lives again. Following the Address given to this Section that summer by Dr. Miles Atkinson [1], it was decided to try his methods of treatment on this group. The results of the decision, which was virtually one of despair, were so encouraging that in order to study the method more thoroughly it was extended to further cases and has now become a routine in the Department.

The series analysed here is of the first 50 consecutive cases. More cases have occurred but they are either still undergoing treatment or the time elapsing since the cessation of therapy has been too short for purposes of review. 28 cases have been male and 22 female. All have been unilateral in type and have exhibited the triad of acute vertigo, tinnitus and deafness in varying degrees of severity. It is interesting to note that 26 of the patients have been wakened from sleep by the onset of vertigo—some on more than one occasion.

Treatment has been carried out according to the results obtained from the histamine skin test described by Atkinson [2]. The salt used for skin testing and therapy has been histamine acid phosphate. This has been prepared in the research laboratory of a large drug firm in Nottingham who produce ampoules of a sterile 1 : 10,000 solution calculated in terms of histamine base, and I should like to acknowledge our gratitude to Sir Jack Drummond for his great help in this connexion.

In the interpretation of the skin test at the beginning of the series two independent judgments of the results were exercised lest one observer might be erroneous in his conclusions. Using normal saline, and in some cases horse serum, as a control in the "untested" arm

and counting no reaction as sensitive, unless one or more "pseudopodia" developed, it soon became evident that reactions were clear-cut and definite and gave rise to no uncertainty. Viewing the reaction by oblique light gave greater relief to the edges of the wheal and pseudopodia. Further, by using an intradermal injection of 0·1 c.c. of a 1 : 10,000 solution of histamine base, instead of 0·1 c.c. of a 1 : 20,000, it was found that wheals and pseudopodia in sensitive cases became more sharply defined, but not larger or longer than when the weaker solution was employed. Similarly, in insensitive cases the edges of the wheals were more raised and sharp, but there was no tendency to develop pseudopodia, nor was the reaction time prolonged.

Of the series, 32 cases gave an initial sensitive reaction, 14 were insensitive, and the remaining 4 were intermediate, i.e. the wheals were approximate to a positive reaction in size and duration but presented a scalloped or budded periphery without the formation of true pseudopodia. I do not think there is any significance in this initial large number of sensitive cases, as the proportion of sensitive to insensitive and intermediate reactions is tending to even out, the larger the series grows.

The sensitive group.—The cases in this group were treated by weekly subcutaneous injections of histamine. The initial dose was 0·1 c.c. of a 1 : 10,000 solution of histamine base. This was increased by 0·1 c.c. weekly, working up to a concentration of 1 : 1,000 solution of histamine base until a reaction was shown by the patient in the form of flushing and headache following the injection. This dose was repeated or increased thereafter on three occasions so that four consecutive reactions were produced. Treatment was then discontinued. This reaction point varied from 0·3 c.c. of the 1 : 10,000 solution to 0·4 c.c. of 1 : 1,000 solution, but so far no patient has required a greater dose than 0·5 c.c. of a 1 : 1,000 solution of histamine base.

On the average most patients felt better by the time they had recieved 0·3 c.c. of 1 : 10,000 solution, in that their attacks of vertigo had decreased in number, intensity and duration, and in some cases the vertigo had ceased altogether. A striking point was the sense of well-being and return of confidence they exhibited.

Regarding the results of therapy to date, I am aware of the shortness of the time factor involved, but without trying to offer any definite conclusions I think that so far they appear to be encouraging.

Of the 32 histamine-sensitive cases 23 have remained free from vertigo since the end of their course of therapy, the time factor being a minimum of six months and a maximum of two years and eleven months. Six cases have relapsed and had further attacks of vertigo, 3 of these after six months' freedom 1 after nine months, and two after one year. 3 of these cases on retesting had become histamine-insensitive and responded to nicotinic acid after histamine made their symptoms worse. The other 3 were still sensitive and responded to further histamine therapy. All have now remained free for periods of over six months.

Three cases have not shown improvement in that they are still subject to attacks of vertigo at intervals of less than two months.

The histamine-insensitive group.—This group has been treated by nicotinic acid. Initially intramuscular injections of 25 mg. to 30 mg. were given daily combined with oral administration of 50 mg. to 200 mg. The balance between individual tolerance and freedom from symptoms has varied greatly, but most patients have been stabilized on oral dosage only, ranging from 50 mg. to 400 mg. daily.

Of the 14 cases thus treated 9 have remained free from vertigo. 4 cases relapsed; 2 of these responded to increased dosage and 2 became worse. According to the skin reaction, these 2 cases had become histamine-sensitive and were relieved of their vertigo by a course of histamine injections.

One case has not improved though apparently remaining in the histamine-insensitive group.

The intermediate group.—In this group of 4 cases 2 have remained symptom free on nicotinic acid therapy and 2 have been unrelieved.

SUMMARY OF RESULTS

Group	Histamine sensitive	Histamine insensitive	Intermediate	Total	%
Vertigo-free ..	23	9	2	34	68
Relapsed ..	6	4	0	10	20
Unimproved ..	3	1	2	6	12

Freedom from vertigo, with its accompanying nausea and vomiting, has been taken as the criterion of improvement in this series. It has been found, however, that improvement in tinnitus and deafness did not take place nearly so frequently.

In 11 cases tinnitus disappeared completely, whilst in a further 9 cases it became less intense though still present. In 30 cases it was unimproved.

Improvement in hearing has been least frequent and only 9 cases have shown an appreciable increase in the hearing level, as checked by audiometry before and after treatment; 41 cases being unaffected.

	No. abolished	%	No. improved	%	No. unaffected	%
Tinnitus	11	22	9	18	30	60
Deafness	Nil	0	9	18	41	82

REFERENCES

1 ATKINSON, M. (1946) *Proc. R. Soc. Med.*, **39**, 807.
2 —— (1946) *J. Laryng. Otol.*, **61**, 344.

Mr. C. S. Hallpike said he was glad to hear Mr. Bateman use the term Ménière's *disease* of the labyrinth. In his view the use of the term Ménière's *disease* was justified and represented a clarification of their ideas on the fundamentals of the disorder.

Ménière's disease was in some ways a very satisfactory condition to treat, but in other ways less so. In the majority of cases satisfactory results could be obtained with judicious sedation with luminal, and nothing else. This meant that anyone who knew this and was capable of diagnosing the condition could treat it with success, and it was in fact so treated by neurologists, general practitioners and others. But when they came to the group of patients who did not do well on this very easy treatment, special chemical methods had to be employed, and again, in his experience, a high proportion did well.

Here the unsatisfying feature was that the patients seemed to do well whichever of these special treatments was selected, and here arose the difficult question of their rationale. If they reverted to the early history of this subject, in particular histamine therapy, they had been told that histamine sensitivity as shown by skin tests meant that the patient was suffering from a labyrinthine manifestation of histamine of which he could be relieved if his resistance to histamine were increased by means of histamine injections. From the point of view of theoretical immunology that had always seemed an unsound notion. Sometimes an allergic basis for Ménière's disease had been suggested, but the manifestations of allergy were multiple, while, on the whole, other allergic phenomena were not seen in Ménière's disease. Further, allergic patients always had their first allergic manifestations early in life, whereas in Ménière's disease the symptoms appeared later. Finally, in allergy there was nearly always a family history of the condition, which was not seen in Ménière's disease.

As regards skin tests, they had been told that if the patients were sensitive to histamine on skin tests, histamine should be given in such cases, but if they were insensitive, they must have nicotinic acid. But the experience of himself and his colleagues at Queen Square did not seem to bear that out (Harrison, M. E. S., 1945, *St. Thomas's Hosp. Gaz.*, **43**, 88). If subjects were negative to histamine with skin tests, this did not seem to forbid successful treatment with histamine, and *vice versa*. Histamine and nicotinic acid were chemically quite different, but they had this in common that they probably produced an increase of the circulatory rate in the labyrinth. It did not seem to matter very much which was given.

In the cases in which he had been concerned, histamine or nicotinic acid was used in accordance with this principle, not much notice being taken of skin tests, and the dose was regulated to produce the maximum circulatory effect. He hoped that further work would be done on the circulation of the fluids in the internal ear, since until more was known of this he did not think there could be any sound basis for either the treatment or the prognosis of this disorder.

Mr. H. V. Forster said that about the year 1910, as a junior physiologist he had been interested in a certain type of intermittent inner ear deafness, characterized by low tone loss, though exacerbations might occur with a sensation of fullness in the ear, clonus of one or other of the intratympanic muscles, and a sense of disorientation, aggravated by movement of the head. It was not until the publication of S. H. Mygind's researches that he felt that a reasonable explanation of these cases of bass inner ear deafness had been offered

The development of successful medical treatment for morbus Ménière, quite apart from the relief of the symptom of vertigo, might preserve the function of the cochlea if such cases of deafness were recognized in the early stages. He had been informed by an American colleague that "dramamine" the now well-known seasickness remedy, was useful in Ménière's disease. He understood that this preparation was a theophyllinate of benadryl and the formula of the Canadian preparation "gravol" had been given to him as follows: Beta-dimethyl-amino-ethyl-benzohydryl ether: 8-chlorotheophyllinate.

He had consulted the medical superintendent of one of the great liner companies, and understood that theophyllin compounds of the anti-histamine drugs available in this country were being tried out for seasickness, with hopeful results from phenergan theophyllinate. He, Mr. Forster, had recently attempted the treatment of a few cases of tinnitus from a small supply of "dramamine". He would be very interested to hear from members of the Section of any experience they might have in the use of these newer modifications of the anti-histamine drugs in morbus Ménière.

Mr. I. Simson Hall said that a similar investigation had been in progress in Edinburgh and he was, therefore, well acquainted with the painstaking and time-consuming character of the work which had been described by the openers.

Mr. Hallpike had already referred to the difficulties in ascertaining the rationale of treatment. He himself had been interested in this subject for a good many years, and on looking through some of the older cases he found that he had tried each routine as it was brought to his notice and that in the case of the salt-free diet system and again in the early histamine treatment, each claimed approximately the same proportion of success. Now there had been added to this the nicotinic acid therapy and a higher percentage of success was reached. Certainly in the series of cases observed in Edinburgh, the observations extending to one year or more, the success as measured in the relief of the vertigo approached 83%. This was for 40 cases.

The difficulty was to assess the value of each treatment as it was introduced. A much greater time would be required before the success of any of these newer treatments could be judged. In an attempt to assess the progress which had been made he had examined the records regarding the references to operative treatment. It seemed to him that instead of accepting the fact that a patient had been free from attack for two years it would be well to see how many cases had been complete failures. Out of a series of 150 to 200 cases he discovered that 20% had been referred for surgical treatment—in other words, they were complete failures. In the last series of cases, from 1946 to a year ago, 15% were complete failures in the sense that they had been referred for operation. In this respect he thought a definite advance in the treatment of Ménière's disease could be claimed for the new methods.

Mr. E. J. Gilroy Glass said that from his own observations he could say that results with Miles Atkinson's treatment had been better than anything he had seen before. He had been particularly struck by the sense of well-being and confidence of the patient.

There were two cases in Mr. Macleod's series which he had not mentioned. They were very alarming at the time though very suggestive in retrospect. Owing to an error in dispensing a batch of histamine, it was made up to 1 : 10 instead of 1 : 10,000, or, in other words, 0·79 gramme instead of 1 mg. Two patients received this injection. Both dropped completely unconscious, with very severe shock, and one was thought to have expired. They both recovered, however, and the interesting thing was that neither of those patients had had any vertigo since. An even more significant thing was that both those patients, who had been extremely deaf, had normal hearing when they recovered consciousness. In one case the normal hearing was maintained for six months and in the other for one month. It was not an experiment to be repeated, but something happened with the histamine which restored the hearing, at least temporarily.

Mr. Terence Cawthorne desired to associate himself with what Mr. Hallpike had said. He was interested in Mr. Simson Hall's figures, because, in their own series of cases, he had found that whatever medical treatment was advised about 50% seemed to be benefited. If one carried on from one medical treatment to another a further 25% came into the satisfactory group—the group, that is to say, in which the attacks were perhaps not cured but were kept at bay. There remained the 25% for which surgical treatment might be required.

There was one aspect of Ménière's disease or hydrops of the labyrinth which deserved consideration. It was sometimes forgotten that this was a disease of the cochlea as well as the vestibule, and he had been struck by the variation of the hearing in these cases of of fluctuating hydrops of the labyrinth. One day the hearing was down, particularly in the low tones, and on another day it was up. One could measure the progress not only by the symptom of vertigo but actually by the change in the hearing which was often easily demonstrable with the audiogram.

From what they had already heard it was quite clear that in many cases medical treatment would give moderately good results, but when it came to the rationale underlying these forms of treatment it was very difficult to be precise or convincing. From time to time further theories might be brought forward; he was quite sure they had by no means got to the end of the story. The advent of dramamine and other histamine products had been mentioned. He had had the opportunity of trying dramamine and another product, phenergan, but it was much too early yet to give the results as he had been using these compounds only for the past three months. In some cases they might produce useful results, while in others the patients said that the cure was almost worse than the disease.

Dr. M. G. Good, speaking from the point of view of a physician, said that he found many a patient suffering from vertigo which was not dependent on an ear condition. The cause was an "idiopathic myalgia", a functional disease of the skeletal muscles. An article on this subject was published in the *Lancet* (1940 (ii), 326) claiming that idiopathic myalgia may simulate visceral, neurological (neuralgia, neuritis) diseases and also vertigo. This "muscular vertigo" is often associated with headache localized by the patient in the occiput—occipital headache. The characteristic "myalgic spots" are regularly found and can be objectively located in one or both trapezius muscles. On appropriate injection of 1–2 ml. of procaine into each myalgic area the complaints disappear very rapidly and permanently.

The concept developed by the speakers that Ménière's disease arises from a disturbance of circulation in the labyrinth appealed to him as a basis of further research. It might, in his opinion, be due either to vasoconstriction—diminished inflow—or vasodilatation, leading to stagnation of the blood and diminished outflow. The common denominator is diminished blood flow, i.e. quantity of blood passing through the unit of tissue per minute, which of necessity leads to a relatively diminished oxygen supply or hypoxia. The relative oxygen deficiency may cause noises by irritation or interference in hearing by hypofunction of the acoustic nerve fibres: it is known that nerves and brain have the highest oxygen consumption.

Dr. Good suggested that the concept of disturbed circulation could be tested experimentally: if nitrites, femergin or other vasodilators produced a relief, even of a temporary nature, the complaints were likely to be caused by vasoconstriction. On the other hand if some of the patients were improved by ephedrine, methedrine, the therapeutic effect would certainly favour the assumption of vasodilatation as the basis of the disease. The discussion had clearly shown that two types of Ménière could be distinguished. It appeared possible to the speaker that the distinction was due to vasoconstriction or dilatation respectively.

Mr. Bateman, in reply, said he did not altogether agree with Mr. Hallpike that most of these patients could be relieved by sedation. Some could be relieved in that way, but he did not think that sedation would put many cases into the "satisfactory" group though it might be that a number would go into the group labelled "improved". As for allergy, he thought they would get into great complications if they started discussing that subject. He did not think, however, that allergy entered into the ætiology of this disease in any appreciable number of cases, but he disagreed with Mr. Hallpike when he said that it did not matter if one failed to differentiate the two groups, positive and negative to the histamine skin test. If therapy were started without carrying out the histamine test one could predict with great accuracy what the histamine test would have shown.

He had seen one or two cases who had been given dramamine for their Ménière's disease. This therapy seemed to come into the same category as sedation. It would produce more relief than most sedatives but it would not produce complete relief such as could often be brought about over a long period with the treatment described in the opening papers. He should have stressed a little more the feeling of well-being of these patients; it was quite remarkable how they would comment on their feeling that they could now do things which they did not attempt before. In other words, they had lost their nervousness and they were able to go back to work and to enjoy it in very many cases.

Observations on the Pathological Mechanism of Conductive Deafness in Certain Cases of Neuroma of the VIII Nerve

By M. R. Dix and C. S. Hallpike

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Until recently it has been our impression that the tuning-fork tests in cases of unilateral deafness due to VIII nerve neuroma conform to the classical pattern of so-called "nerve deafness". That is to say, the sound of the fork with Weber's test is typically referred to the normal ear, Rinne's test is positive, and perception with the absolute bone conduction test is reduced. Should the Rinne be negative it is a false negative; that is to say, the apparently good perception by bone conduction with the affected ear is due to the transfer of the vibrations to the opposite cochlea, through which it is in fact perceived. This well-known fallacy is recognizable and can be excluded by abolishing the perception by the normal ear of this bone-conducted sound by means of an air-conducted masking sound.

In the course of a previous communication made to this Section (*Proc. R. Soc. Med.*, 1949, **42**, 527), we said that there were some exceptions to this rule, in which a true negative Rinne appeared to be present in the ear affected by the neurofibroma and it is this point to which we return to-day.

So far as we know, all writers who have published their observations upon the tuning fork tests in the deafness of VIII nerve neuroma are in agreement that they conform to the classical pattern of nerve deafness and they have little more to say on the subject. All observers except one, T. H. Just, who in an excellent paper published in 1930 (*Proc. R. Soc. Med.*, **23,** 722) insisted that in certain cases of VIII nerve neuroma the negative Rinne is no artefact, but a true and, as he described it, "disturbing phenomenon".

In our own experience at Queen Square we have encountered a number of cases of this kind. In 2 of these death followed surgical intervention carried out soon after our examination and we were able, through the good offices of Dr. Greenfield, to carry out a histological examination of the temporal bones.

It is the purpose of this communication to describe our findings, and explain how we think they account for this interesting, and as Just described it "disturbing" anomaly—the negative Rinne—in the tuning-fork test results.

The first of our subjects was a man of 57, and the second a woman of 47. They were under the care of our colleagues at Queen Square, Drs. Walshe and Carmichael, to whom we are greatly indebted for permission to investigate the cases and to make use of the clinical notes. The findings in both were characteristeric of an VIII nerve neuroma.

Case I.—A. E., male, aged 57, under the care of Dr. F. M. R. Walshe.

Complaint: Pain behind the left ear and deafness, left ear, four years. Numbness left side of face and unsteadiness in walking, seven months. He had recently experienced difficulty in winking his left eye, and in tasting things on the left side of his tongue.

The pain behind the left ear had been intermittent, never very severe, and never lasted for more than a few hours at a time. The deafness had never been accompanied by tinnitus and in the patient's opinion was quite slight. The difficulty in walking was constant but not severe. He tended to run into things on his left side and was unable to turn round quickly without losing balance. He had never actually fallen or needed support, and there had never been any giddiness.

Neurological findings.—General condition: alert and co-operative.

Visual fields full, fundi normal. Pupils normal. External ocular movements full. Corneal reflexes: right brisk, left absent.

Diminished sensation to cotton-wool, pin-prick and cold over the whole distribution of the left V nerve, including the tongue and hard palate. Some weakness of the left temporal muscle. Slight weakness of the left side of the face of the lower motor neurone type, with impairment of taste over the anterior two-thirds of the tongue on the left. IX, X, XI and XII cranial nerves normal.

Motor system: Normal except for very slight inco-ordination with the heel/knee test on left side.

Neurological diagnosis (Dr. F. M. R. Walshe).—Left VIII nerve neuroma.

X-rays: Normal skull. No evidence of enlargement of the internal auditory meatuses. Ventriculography: Slight, symmetrical hydrocephalus. The aqueduct was lengthened and bowed slightly backwards. The fourth ventricle was displaced to the left, and the anterior border rotated to the right. *Conclusion.*—A left cerebello-pontine angle expanding process (Dr. J. W. D. Bull).

C.S.F. lumbar puncture: Pressure 160 mm. Cells: White nil. Red 5 per c.mm. Protein 260 mg. per 100 c.c.

Otolaryngological examination.—Hypo-æsthesia to pin-prick on left side of soft palate, left side of tongue and left inferior turbinate. Tympanic membranes normal. Other findings normal.

Cochlear function.—Whisper (normal 30 ft.): Left, at meatus. Right > 20 ft. Weber (512 c.p.s.) referred to left. Rinne, Left: Negative with masking of right ear. (The masking procedure was carried out by means of a speaking tube through which an assistant applied to the right ear a continuous sh-sh-ing sound.)

Pure tone audiometry (air conduction only).—With the left ear there was an approximately uniform loss (50 db.) for all tones up to 2,048 c.p.s. Above this frequency the loss increased and 8,192 cycles could not be heard at the maximum output of the audiometer (90 db.). There was also a slight loss of hearing in the right ear (Fig. 1A).

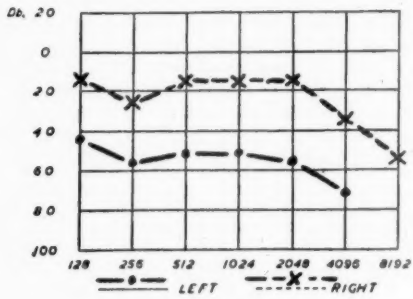


FIG. 1A.—Case I.

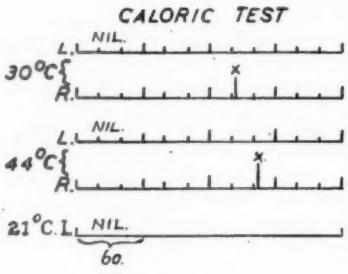


FIG. 1B.—Case I.

Vestibular function.—Posture and gait: A marked tendency to drift to the left when standing or walking with the eyes closed.

Spontaneous nystagmus: With the head erect, first degree vestibular nystagmus was present both to the left and to the right, that to the left being of greater amplitude than that to the right.

Positional nystagmus: In the supine position with the head back and to the left second-degree positional nystagmus of the central type was present to the right. Optokinetic nystagmus: This was markedly diminished to the left, particularly at higher speeds of the drum.

Caloric responses: Complete abolition of the left responses with some directional preponderance to the right of the right responses (Fig. 1B).

Summary of otological findings.—Cochlear function: Partial deafness of the left ear; conductive type. *Vestibular function*: Spontaneous nystagmus. Positional nystagmus of the central type and abnormality of optokinetic nystagmus. Complete loss of the left caloric responses.

Otological diagnosis.—Left VIII nerve neuroma.

Operation.—The left cerebello-pontine angle was explored on 28.10.46 by Mr. Wylie McKissock. The left cerebellar hemisphere was lifted and retracted medially to reveal a small typical acoustic neuroma lying in the cerebello-pontine angle. A complete extracapsular removal was carried out.

Following the operation the patient recovered partial consciousness but became drowsy two hours later and died in coma on the following day.

Post-mortem.—The tumour cavity lay between the upper and lower halves of the cerebellum and indented the left side of the pons in its lower half. The tumour had been completely removed. Histological examination showed it to be a neurofibroma of rather unusual histology. Examination of the pons showed almost complete hæmorrhagic destruction of the tegmentum passing inwards as far as the mid-line against the ependymal lining and extending backwards along a line running from the central fovea of the ventricle to the outermost part of the ventral surface.

The temporal bones were removed and on superficial examination appeared normal apart from a moderate degree of enlargement of the left internal auditory meatus.

CASE II.—G. B., female, aged 47. Under the care of Dr. E. A. Carmichael.

Complaint.—Deafness in the right ear three years. Suboccipital headaches six months. Attacks of vomiting with nausea three months.

The deafness was of gradual onset. Recently it had become progressively worse and had been accompanied by "a noise like a railway engine" all over the head. For a short time before admission she had been rather unsteady with a tendency to deviate to the right. No history of giddiness, although objects sometimes tended to "sway up and down".

Neurological findings.—Alert and well orientated in space and time. No impairment of memory. Visual fields full. Mr. Williamson-Noble reports: "Slight blurring of both discs but within physiological limits." Pupils normal. External ocular movements full. Corneal reflexes: Left present, right absent. Loss of sensation to pin-prick and cotton-wool over the facial distribution of all three divisions of the right V nerve but no motor weakness. Slight weakness of the right side of the face of the lower motor neurone type, and slight fibrillation of the right side of the tongue with deviation to the right. Motor system: Upper limbs—some loss of tone and inco-ordination of the right hand and right leg. Loss of sensation to pin-prick over the second cervical segment. Reflexes: Rt. K.J. > left K.J.

X-rays (including Towne's projection): Normal skull. Ventriculography: The fourth ventricle was dilated and displaced upwards and to the left, the displacement being most marked at its lower end. The appearances were those of a space-occupying lesion in the posterior fossa on the right side.

Neurological diagnosis.—? Right VIII nerve neuroma. C.S.F.: Pressure 80 mm. clear and colourless. Cells: 1 lymphocyte per c.mm. Protein 300 mg. per 100 c.c.

Otolaryngological examination.—Tongue, palate, pharynx and larynx normal. Nose and naso-pharynx normal. Tympanic membranes: Left—imperforate, marked atrophic changes. Right—imperforate, slight atrophic changes.

Cochlear function: Whisper (normal 30 ft.). Left: > 20 ft. Right: At the meatus. Weber (512 c.p.s.) referred to left. Rinne: Left positive. Right negative, with masking of the left ear. (Masking as in Case I.) Absolute bone conduction: Right slightly reduced.

Pure tone audiometry (air conduction only). Left normal. Right: There was a severe loss chiefly affecting hearing for the highest and lowest frequencies (Fig. 2A).

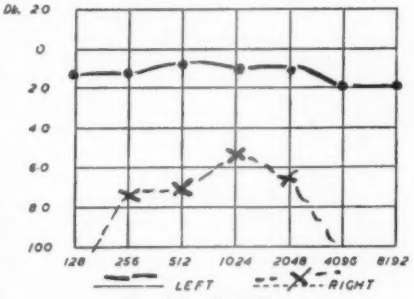


FIG. 2A.—Case II.

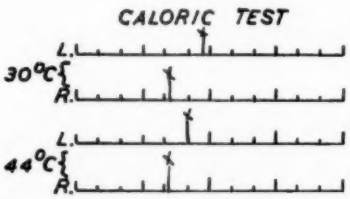


FIG. 2B.—Case II.

Vestibular function: Spontaneous nystagmus: With the head erect, first-degree vestibular nystagmus was present both to left and right, that to the right being slower than that to the left. Positional nystagmus: In the supine position, second degree positional nystagmus to the left was present with the head back and to the right. Optokinetic nystagmus: The response to the left was abolished. Caloric responses: A well-marked diminution of the right responses to both cold and hot stimulation. No directional preponderance was present (Fig. 2B).

Summary of otological findings.—Cochlear function: Partial deafness of the right ear. The deafness was, in some respects, characteristic of a conductive lesion.

Vestibular function: Spontaneous nystagmus, positional nystagmus and abnormality of optokinetic nystagmus. Reduction of the right caloric responses.

Otological diagnosis.—Right VIII nerve neuroma.

Operation.—The right cerebello-pontine angle was explored on 7.3.46 by Mr. Wylie McKissock. On retraction of the right cerebellar hemisphere a typical and fairly soft acoustic neuroma was exposed. The surface was coagulated and a considerable amount of tissue removed with the aid of a scoop and suction. Extracapsular removal was then completed.

The patient died on the following day. At post-mortem, hæmorrhagic changes were found in the right side of the pons with flattening of the right middle cerebellar peduncle. A small nodule of tumour remained in the right internal auditory meatus which was not enlarged. Histological examination of the tumour removed revealed a typical acoustic neurofibroma. The temporal bones were removed and on superficial examination appeared normal.

PATHOLOGICAL EXAMINATION OF TEMPORAL BONES

The temporal bones of both subjects were fixed in 10% formalin and embedded in celloidin. Serial sections were then cut in the usual way.

In the course of this procedure it is normally possible to see a great deal of the finer labyrinthine structures through the clear medium of the celloidin. With the affected temporal

bones of these two subjects, however, the labyrinthine structures were obscured by a fine "coagulum" or gel formation which was evenly distributed throughout and completely filled all the perilymph and endolymph spaces. It was much less dense than that found in labyrinthitis and much more even in its texture and distribution than the exudation which commonly occurs in this condition and indeed in any pathological condition of the labyrinth that we have previously examined. The nature of the abnormality is illustrated in Figs. 3 and 4. These are photographs of two celloidin blocks taken during the course of section cutting. Fig. 3 shows a normal temporal bone in which the normal cavities and membranes of the labyrinth can be clearly seen. Fig. 4 shows the affected temporal bone of a patient with an VIII nerve neuroma in which the naked-eye appearances closely resembled those seen in the 2 cases which form the subject of this paper. The obscuration of the membranes and labyrinth spaces is very evident.

When the sections had been cut and stained in the usual way, with hæmatoxylin and eosin, we were further interested to observe that no sign of the "coagulum" so evident during the process of section cutting could be observed. The histological features of the two cases are shown in Figs. 5 and 6. In both, the external auditory meatuses and the middle ears are normal. The internal auditory meatuses are distorted and occupied by the remains of the neuromata. In the cochleæ, higher magnifications reveal degenerative changes in the nerve fibres and cells of the spiral ganglia. In neither of the sections shown, however, is it possible to appreciate that all the labyrinthine cavities are completely occupied by the homogeneous "coagulum" to which reference has been made. The appearance of the sections was next studied without staining and with dark ground illumination. Under these conditions the presence of the "coagulum" could be readily seen. Figs. 7 and 8 are photomicrographs of unstained sections serially consecutive with those shown in Figs. 5 and 6. They are photographed at the same magnification and with dark-ground illumination. In both, the fine "coagulum" can be seen uniformly filling every part of the labyrinthine spaces. The abnormality of this appearance is illustrated by comparison with Fig. 9 which shows the appearance of a normal labyrinth prepared and photographed under identical condition.

Discussion

It is well known that the labyrinthine spaces are the site of a variety of exudates and transudates, resulting not only from VIII nerve tumours but from many other pathological conditions. Nearly always, however, the distribution and texture of the resulting "coagula", if this term be permissible, are much more irregular than that revealed in the present 2 cases. In addition, it is usually demonstrable quite readily with hæmatoxylin stain. It is justifiable, therefore, to regard the present findings as quite unusual and our next task is to consider how they could be applied to the explanation of the equally unusual but clinically important finding of deafness of the so-called conductive type.

The physical problems concerned with hearing by air and bone conduction, though complex, still seem capable of explanation, in their essentials, in terms which can have changed very little since the days of Bezold. It is known, for instance, that in hearing by air conduction by far the greater proportion of the sound energy reaches the basilar membrane by way of the conducting mechanism which includes not only the tympanic membrane and ossicles but also the fluid contents of the labyrinth. In the case of hearing by bone conduction, while a proportion of the sound energy still reaches the basilar membrane by way of the conducting mechanism, other and more direct pathways through the bony cochlear walls are available.

It follows, therefore, that lesions which disturb the conducting mechanism will have their chief effect on hearing by air conduction; hearing by bone conduction will be affected to a smaller extent. In this way we have the poor hearing by air conduction and the relatively good hearing by bone conduction which are typical of conductive deafness and underlie its characteristic tuning-fork reactions, in particular the negative Rinne. The mechanical characteristics of the middle-ear mechanism are, of course, bound up with its function of overcoming, by virtue of its impedance-matching properties, the severe attenuation which normally occurs when airborne sound enters a fluid medium. The efficiency of this function, however, is necessarily dependent upon normal physical conditions of the labyrinthine fluid, and we think it likely in this connexion that the abnormal histological appearances of this fluid described in our 2 cases connote the existence during life, if not of an actual coagulum, at any rate of some considerable change of its density. The suggestion is therefore made that this density change brings about in turn a mechanical change in this, the terminal component of the conductive mechanism, which disturbs its performance as a whole in a manner which is essentially comparable to that brought about by better-known lesions of its other components, as, for example, middle-ear disease or otosclerosis. As

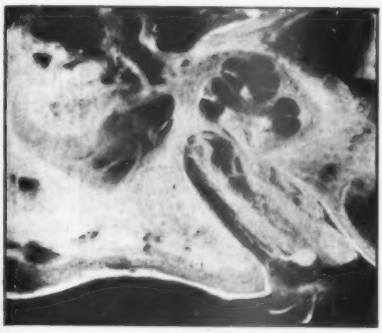


FIG. 3.

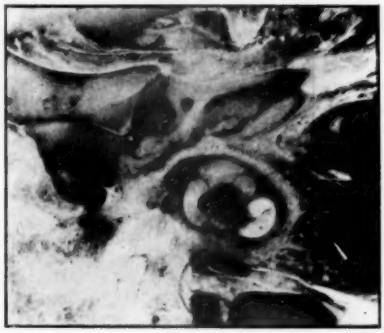


FIG. 4.

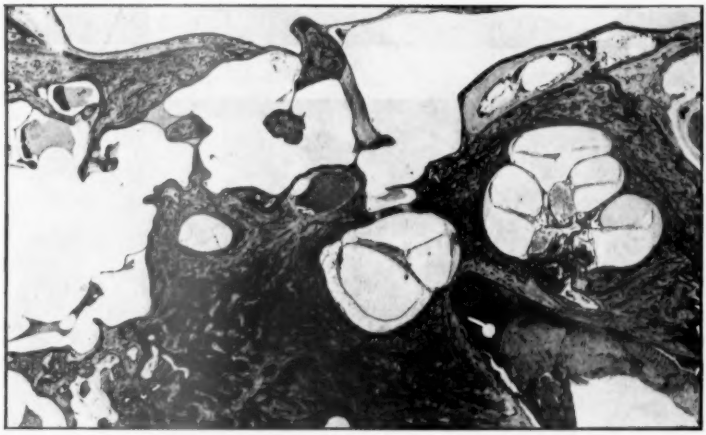


FIG. 5.

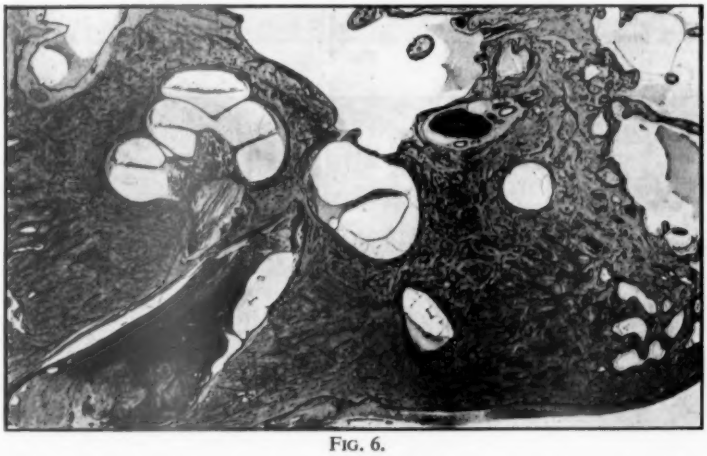


FIG. 6.

M. R. DIX and C. S. HALLPIKE: *Observations on the Pathological Mechanism of Conductive Deafness in Certain Cases of Neuroma of the VIII Nerve.*

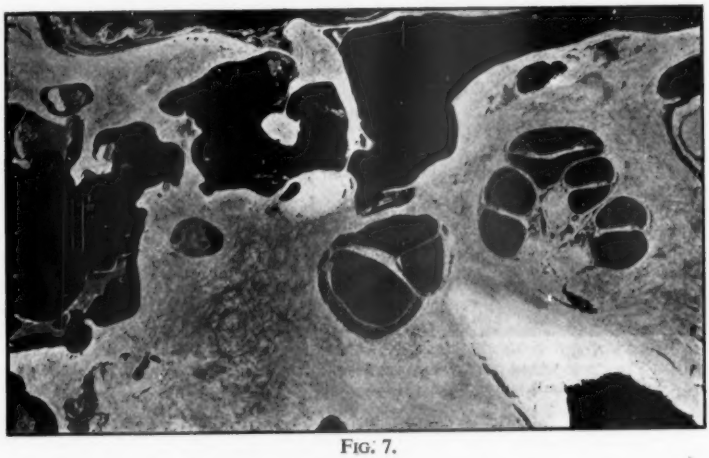


FIG. 7.

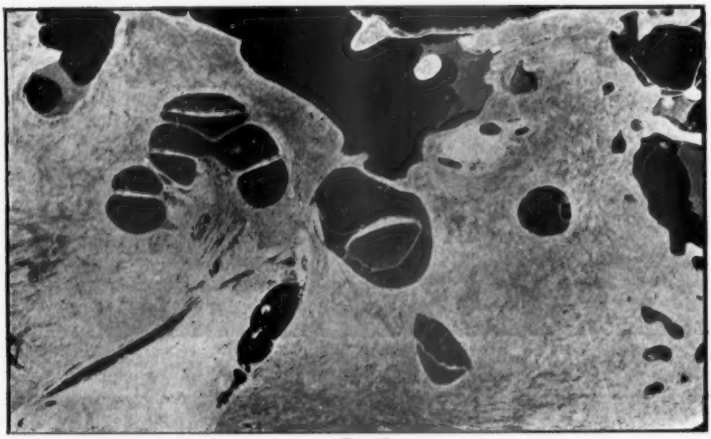


FIG. 8.



FIG. 9.

M. R. DIX and C. S. HALLPIKE: *Observations on the Pathological Mechanism of Conductive Deafness in Certain Cases of Neuroma of the VIII Nerve.*

a result, the consequent deafness is of the same conductive type. Loss of hearing by air conduction is severe, hearing by bone conduction relatively good and the Rinne test negative.

If this suggestion be acceptable, then it follows that a conductive element would also be likely to occur in the deafness which results from other forms of labyrinthine disease which are characterized by similar changes in the labyrinthine fluid. Of these, neuro-labyrinthitis, in particular that secondary to meningitis, may be taken as a likely example. In the majority of such subjects the deafness, which is due in large part to the destruction of the nervous elements, is extreme both by air and bone conduction, and no qualitative tests are therefore possible. We have, however, encountered some cases of this kind with partial deafness in whom the tuning-fork tests could be carried out with reasonable accuracy, and in a few of these we have been interested to note the presence of a true negative Rinne. A summary of the clinical features of three such cases is appended.

P. I., aged 10.

History.—Meningitis aged 3. Deafness in left ear noticed at age of 8.

Examination.—Tympanic membranes normal. Rinne (512 c.p.s.): Left negative with masking of right; right positive. Absolute bone conduction (left) much reduced with masking of right.

Audiograms.—(Tests of left ear carried out with masking of right ear, *see below*, Figs. 10A, 10B.)

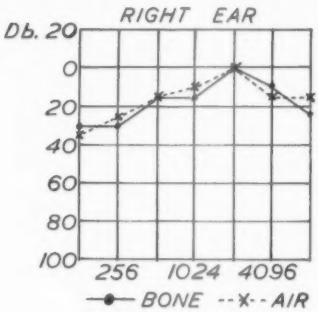


FIG. 10A.

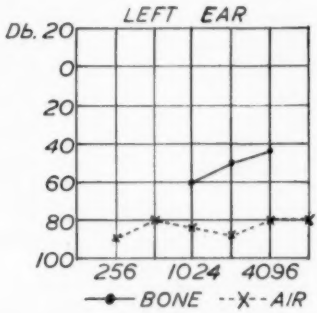


FIG. 10B.

A. P., aged 32.

History.—Deaf since meningitis aged 2.

Examination.—Tympanic membranes normal. Rinne (512 c.p.s.): Left negative; right false negative. Absolute bone conduction (left) much reduced. (*See* Fig. 11.)

R. T., aged 8.

History.—Maternal rubella at second month. Deafness noticed at age of 5.

Examination.—Tympanic membranes normal. Rinne (512 c.p.s.): Left negative; right negative. Absolute bone conduction grossly reduced left and right. (*See* Fig. 12.)

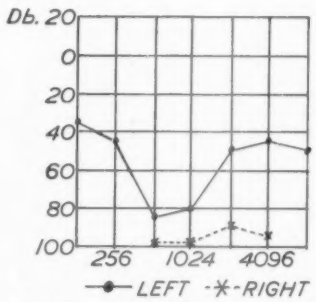


FIG. 11.—Audiogram of Case A. P. (Air conduction.)

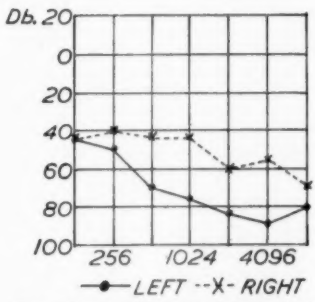


FIG. 12.—Audiogram of Case R. T. (Air conduction.)

A clinical feature of all 3 cases, and one of importance in clarifying the diagnosis, was the reduction of perception with the absolute bone conduction test, a finding to which we attach clinical importance in the diagnosis of disease of the cochlear nervous elements. In 2 of the 3 cases also (P. I. and A. P.) a gross abnormality of the caloric responses was also present. In the third case (R. T.) the caloric tests were not carried out. It seems, therefore

necessary to stress the clinical value in these difficult cases, both of the absolute bone conduction and the caloric tests, since they make so plain that co-existent with the conductive element of the deafness a perceptive element is also present.

In conclusion, it may be said that although the conception of the labyrinthine fluid as constituting an element of the conductive mechanism is not a new one, this would appear to be the first occasion on which it has been possible to give it the support of direct anatomical and clinical observations.

Mr. F. C. Ormerod recalled a discussion on acoustic nerve tumours by this Section in 1923 when the negative results of the Rinne test were mentioned but not discussed at any length. In 1929, T. H. Just definitely described the true negative Rinne and in 1934 Albert Gray described the histology of the temporal bones of two cases of bilateral acusticus nerve tumours (*Proc. R. Soc. Med.*, **27**, 1179). Both patients, one under the care of the late Professor de Kleijn and the other under the care of the speaker, showed a negative Rinne test. In both cases Gray demonstrated otosclerotic changes in the neighbourhood of the oval window and he felt that this explained the negative Rinne. He felt also that the occurrence of otosclerotic changes following acusticus tumours confirmed his theory as to the vasomotor origin of otosclerosis. The findings were illustrated in the second volume of Gray's Atlas of Otology.

Mr. T. A. Clarke asked Mr. Hallpike how the coagulum found in cases of VIII nerve tumour with apparent negative Rinne differed from that found in similar cases with the usual finding of a positive Rinne. It was agreed that perfect masking of the good ear had still to be achieved in testing bone conduction on the diseased side. Could any failure in masking account for the apparent negative response described in the Rinne test in these cases?

Mr. I. Simson Hall said that Mr. Hallpike's findings had interested him enormously. On one occasion during the fenestration operation, in a case of fairly extreme deafness, he opened the labyrinth and found a condition he could not understand. The bone surrounding the canal was rather soft and the outlines were blurred completely. He supposed that the patient must have had a labyrinithitis, but it now occurred to him that Mr. Hallpike's explanation might have been the correct one. The operation was a complete failure.

Mr. Philip Scott said that he was stimulated, on getting notice of this Paper, to refer to some of his notes, and now he was stimulated again to go back and look at his sections. In the sections at which he had had an opportunity of looking he was dissatisfied in one particular case with the negative Rinne. That case did have a noticeable coagulum throughout the section. He now intended to re-examine the section in the light of the observations of Mr. Hallpike and of some others.

Mr. Hallpike, in reply, said that when they began to encounter these cases with evidence of conductive deafness they used to think of the likelihood of an associated otosclerosis, but as they had the opportunity of examining further material they never found otosclerosis, and in the cases shown that day the stapes footplates and middle ears were normal.

Mr. Clarke had asked how this particular coagulum compared with the coagulum which occurred not uncommonly in other conditions of the labyrinth. Generally speaking, such coagulum was much more scattered and less homogeneous than that found in the 2 cases under discussion. As to guaranteeing the efficiency of masking, this it was difficult to do.

He had been very much interested in what Mr. Simson Hall had told them, because in some cases of deafness in children of 5 to 10 years of age the diagnosis of juvenile otosclerosis was sometimes made with some confidence on the basis chiefly of a negative Rinne test. It seemed to him that had caloric and absolute bone conduction tests been done in Mr. Simson Hall's case a different view might have been taken of the diagnosis.

Section of Orthopædics

President—NORMAN CAPENER, F.R.C.S.

[*October* 4, 1949, *contd.*]

Bone Dystrophy of Unknown Ætiology (Presented for Diagnosis).—H. H. LANGSTON, F.R.C.S.

F. H., aged 48, was referred to the Orthopædic Out-patient Department on account of painful knees.



FIG. 1.—F. H.

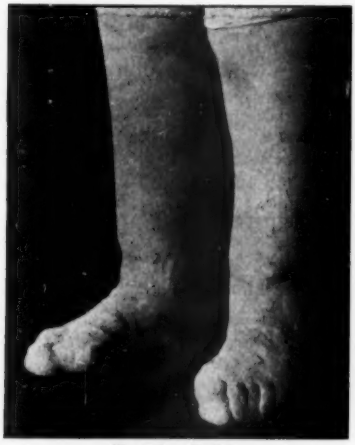


FIG. 2.—F. H.



FIG. 3.—D. S.



FIG. 4.—D. S.

FIGS. 1–4.—Show bone dystrophy of unknown ætiology in a brother and sister, illustrating marked clubbing of fingers, lower ends of tibiæ and toes.

On examination.—Healthy man with no evidence of cardiac or pulmonary abnormality. There was present marked bilateral enlargement of the lower ends of the radius and ulna, of the femora and of the tibiæ, with clubbing of the fingers and toes. Patient stated that the clubbing had been present for as long as he could remember, and was quite definitely present in adolescence.

X-rays show marked enlargement of the lower ends of the radii and ulnæ, femora and tibiæ. This enlargement appears to be due to long-standing periosteal new bone formation. On the surface of the bone around the enlarged ends are numerous small bony projections.

Pathological investigations.—Serum phosphate, inorganic 4·5 mg.%, serum calcium 9·9 mg.%, serum phosphatase—acid 0·6 K. and A. units, alkaline 4·8 K. and A. units.

W.R. negative. Complete and differential blood-count: No abnormality.

Family history.—Patient is one of eight brothers and three sisters. One sister (D. S.), aged 58, has a precisely similar bone dystrophy (*see* photographs and X-rays). All brothers and sisters have multiple cutaneous fibromata. The affected sister states that the condition in her case has also been present for as long as she can remember. Both patients have led healthy active lives and have suffered no inconvenience from the disability until the present time. Both are now beginning to develop symptoms from the onset of osteo-arthritis.



FIG. 5.—F. H.



FIG. 6.—D. S.

FIGS. 5–6.—Skulls of F. H. and D. S. Note the angle present at occipito-parietal suture.



FIG. 7.—F. H.



FIG. 8.—D. S.

FIGS. 7 and 8.—Hands of F. H. and D. S., illustrating clubbing.



FIG. 9.—F. H.



FIG. 10.—D. S.



FIG. 11.—F. H.



FIG. 12.—D. S.



FIG.—13.—F. H.



FIG. 14.—D. S.

FIGS. 9–14.—Long bones of F. H. and D. S., illustrating marked clubbing, particularly of the lower end of the radius and tibia with irregular periosteal new bone formation.

Sir Thomas Fairbank said he had seen this case and the man's sister some months ago with Mr. Langston and had since tried to find a comparable published case. A useful paper was one published by Uehlinger under the title Hyperostosis Generalisata mit Pachydermie (Idiopathische Familiäre Generalisata Osteophytose) in Virchow's *Archiv. Path. Anat. Physiol.*, 1941, **308**, 396. Though Uehlinger's case is not strictly comparable with the present case—the bones are coarsely striated in addition to the hyperostosis—he discusses a variety of published cases, a few of which are of interest. Mr. Langston's case was certainly not one of hypertrophic osteoarthropathy in his opinion.

NOTE.—On further research, the cases which seem to show the closest similarity to Mr. Langston's are a brother and sister reported by Mankowsky *et al.*, *Fortschr. Röntgenstr.*, 1934, **50**, 542.—H. A. T. F.

[*November* 1, 1949]

Leri's Disease (Melorheostosis).—G. P. ARDEN, F.R.C.S.

Female, aged 13 years.

Family history.—Nothing relevant. I saw this patient two years ago, on account of hallux rigidus of the left big toe. The X-ray photograph of the foot showed a streaky condensation of dense bone (Fig. 3). This was also found to involve the left tibia, the femur, and a small portion of the acetabulum (Figs. 1, 2A, 2B). On examination there was



FIG. 1.



FIG. 3.



FIG. 2A.



FIG. 2B.

FIG. 1.—Streaky condensation of dense bone running up neck of femur from the shaft, also involving upper margin of acetabulum. Some cortical thickening inner side of left femur just below lesser trochanter.

FIG. 2A.—Dense striæ of bone in upper tibia crossing epiphyseal line into external tibial condyle affecting upper fibular epiphysis, patella and femur. Several rounded areas of dense bone in both lateral tibial and femoral epiphyses.

FIG. 2B.—Streaky condensation in lower femur, patella and upper tibia.

FIG. 3.—Left foot showing streaky condensation of bone affecting tarsal bones and lower tibia.

limitation of movement, not only of the big toe-joint, but of the ankle, knee and left hip-joint and two inches shortening of the left leg. The patient had had no pain but only limitation of movement. This condition appears to begin in childhood and is more common in males than females, it usually affects one limb. One case has been described as Leri's disease and also osteopoikilosis. Another complication which is sometimes seen is sclerodermia of the skin, but there was no sign of that in this case. The condition tended to progress when followed up for some years. The treatment in this case had merely been to raise the left shoe by 2 inches and a Kellar's operation had been performed on the left big toe.

The President said that he found it difficult to accept this case as a straightforward one of melorheostosis. The intra-osseous condensations in the tibia suggested Albers-Schönberg's disease.

Osteopoikilosis Affecting Right Foot and Other Bones.—G. P. ARDEN, F.R.C.S.

This patient was referred to me by Mr. Lovelock-Jones as a case of osteopoikilosis.

Female, aged 36, first came to the out-patients' department with swelling of the right ankle of a few weeks' duration. The X-ray picture revealed osteopoikilosis (Figs. 4A and 4B). She had had no trouble previously and X-rays of her small daughter showed a normal condition. Further X-ray examination revealed generalized bony changes mainly affecting both feet, hands, hips and shoulders (Figs. 1, 2, 3). There was some œdema of the right ankle, otherwise the patient was quite fit.

This condition was first described in 1905, but much more fully in 1915 by Albers-Schönberg. This again was more common in males than females. There was some tendency for the spots to join up and form striæ. The condition may progress or remain stationary. The œdema of ankle in this case suggested an early sclerodermia, but I can find no reference to this complication in other cases.



FIG. 1.—Several areas of dense bone in neck of both femora tending to form striæ. Both ischii also affected.



FIG. 2.

FIG. 2.—Few scattered dense areas in head of humerus and acromium.

FIG. 3.—Scattered areas of dense bone mainly affecting the carpal bones. (Both hands affected.)



FIG. 3.



FIG. 4A.



FIG. 4B.

FIGS. 4A and 4B.—Multiple small rounded areas of condensation affecting tarsal and metatarsal bones.

Sacral Spina Bifida and Meningocele.—K. I. NISSEN, F.R.C.S.

A cobbler, aged 43. He had a sacral spina bifida and a large meningocele with complete urinary incontinence. There was severe bilateral talipes equino-varus, with chronic ulceration of the soles of both feet (Fig. 1). The ulcers on the left side commenced at 23 and on the right at 34; they caused recurrent but almost painless cellulitis of both feet. Apart from its bulk the meningocele itself gave little trouble, although pressure upon it caused headache. His rubber urinal was liable to spill and he also suffered from deafness.



FIG. 1.

FIG. 1.—Severe bilateral talipes equino-varus with chronic painless ulceration.

FIG. 2.—Showing meningocele and double below-knee amputation.



FIG. 2.

When first seen in January 1949 he was severely disabled on account of his grossly deformed and deeply ulcerated feet. After yet another flare of infection, the patient agreed to bilateral below-knee amputation. This was done in July and in August, and in September the patient was fitted with temporary Durestos pylons (Fig. 2). He walked well in a few days, possibly because he was used to partly insensitive limbs which afforded him little information. Standard below-knee limbs from Roehampton, and a hearing-aid for severe deafness, are both on order. In view of imperfect bowel control, transplantation of the ureters could not be entertained, but an improved (Donald Rose) urine-collecting apparatus has proved very satisfactory. This patient had become almost a social outcast, but the improvement in his general health and mental outlook is already remarkable.

The President said he was rather interested in Mr. Nissen's case of lumbar meningocele. He recalled that Sir Thomas Fairbanks told him on one occasion that he had long ceased to operate on spina bifida. Miss Forrester-Brown recently had demonstrated a cup-shaped device made of Perspex which she placed over such lesions in babies to give protection. The meningoceles had regressed, and even, in a certain number, had disappeared.

Spondylitis Ankylopoietica with Deformity of the Cervical Spine.—K. 1. NISSEN, F.R.C.S.

This man, a street-trader, aged 52, had used a motor-chair for many years, but found that his restricted range of vision made driving unsafe. Three plastic cervical collars had been made with a useful degree of correction of the cervical deformity and with loss of painful fatigue of the neck muscles (Fig. 1).



FIG. 1.—The deformed cervical spine supported by a polyethylene collar.

Dr. John Scales: Mr. Nissen's cases illustrate the use of two plastic materials—Durestos and polyethylene. The former material is used in aircraft construction and the latter for electrical insulation and plumbing.

Durestos arrives in fairly rigid sheets. When damped with water the material becomes very malleable and can be stretched to cover any shape. A positive plaster cast is needed for moulding the material, which cannot be applied directly to the patient. It is "cured" by heating in an oven at 70° C., after which there is no danger of contact dermatitis.

To make an above-knee pylon like the one exhibited to the Section, about four thicknesses are used, but over the ischial weight-bearing area, up to ten thicknesses; the bucket and peg down to the heel are made in one. The finished pylon, weighing only some two pounds, may need to be weighted for better control.

The other material, polyethylene, a polymer of ethylene, is a typical thermoplastic material. A flat sheet is taken and tailored roughly to shape. For a cervical collar the back and front parts are cut out and put on to an asbestos board. The material is heated up to 119° C. in a gas-oven; when it becomes clear, it is ready for moulding. Reinforcing strips of the same material can be put on if required and readily fuse at 119° C. Polyethylene is waxy in appearance and feel, and is resilient. It does not tear or break, having no internal stresses when moulded. Ventilation is obtained by drilling holes.

Osteomyelitis of the Acetabulum with Intra-pelvic Protrusion of the Head of the Femur.—K. I. NISSEN, F.R.C.S.

Woman, aged 50. She developed a staphylococcal infection of the inner wall of the acetabulum and of the hip-joint in East Africa. By the time of her arrival in England, the head of the femur had entered the pelvis (Fig. 1), an abscess in the groin had left a chronic sinus, the leg was grossly œdematous, and the blood picture showed a severe toxic anæmia. The anti-α-hæmolysin titre was 20 international units, a very high figure.

The head and neck of the femur were excised through an incision which allowed access both to the hip and to the head lying beneath the iliopsoas muscle. Post-operatively skeletal traction through a tibial pin was used, with care to avoid external rotation. By the fourteenth day the sinus had closed, the wound was healed, and the range of flexion was 100 degrees. As the capsule at operation had been half an inch thick, it was thought that fibrosis would give stability of the pseudarthrosis sufficient to avoid the use of a caliper.



FIG. 1.



FIG. 2.



FIG. 3.

FIG. 1.—Showing the intrapelvic protrusion of the head of the femur through the softened inner wall of the acetabulum.

FIG. 2.—Four months after excision of the head and neck, the trochanters were raised and the pseudarthrosis was unstable.

FIG. 3.—Four months after a plate osteotomy and two months of weight-bearing the pseudarthrosis appears stable.

After three months of crutches and non-weight-bearing, however, the trochanter was riding high and the joint was obviously unstable (Fig. 2). The plated osteotomy described by Batchelor was therefore performed and, with tibial traction as before, bone union was sound at eight weeks. The range of passive flexion on return to East Africa was 110 degrees and the range of abduction and adduction was fully equal to that on the normal side (Fig. 3). Shortening was 1¼ inches, and the patient walked well with one stick and a raised heel. The physical treatment after each operation was simplified by using a method of skeletal traction which has been found to have a number of practical advantages (Fig. 4).

The apparatus is based upon the long U-loop used by Tulloch Brown of Glasgow, which is a four-foot length of aluminium bar, ⅛ inch by ¼ inch in cross section, bent into a U with an inside width of 4½ inches. The end of each side bar has several holes drilled in a zig-zag order over a length of some 3 inches. These holes allow the side-bars to be threaded over the ends of the Steinmann pin outside the fixed bushes of a Steinmann stirrup. The series of holes makes allowance for variation in the length of the lower leg, but, more important, permits the U-loop to be inclined to one or other side in order to give equal clearance at the malleoli. With the calf supported by slings, suspension is obtained from a cord attached to the stirrup and traction from a horizontal cord attached to the end of the U-loop.

The traction apparatus in use at Stanmore has the following modifications (Fig. 4):

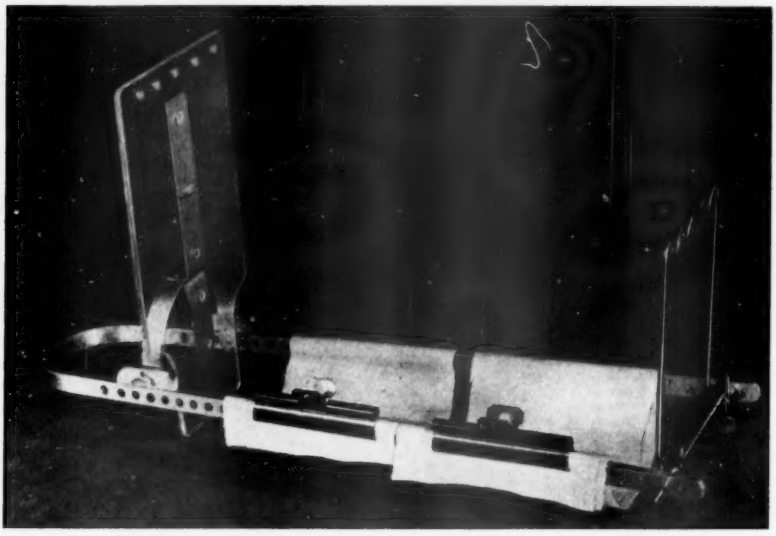


FIG. 4.—Tulloch Brown's U-loop with adjustable foot-piece and modified Steinmann stirrup.

(1) A detachable foot-piece has been designed which can be set in any pair of a number of opposing holes drilled $\frac{1}{2}$ inch apart. The foot-plate is of Perspex and measures 12 by 6 inches. It is attached to a semi-circle of spring steel which has at either end a stud to fit the holes and a horizontal lug fitting along the upper margin of the side-bar to restrain rocking. The foot-piece, which is mainly for use at night, gives flat support to the forefoot, and being springy, is excellent for resisted exercise of the calf muscles. A series of holes along the top of the foot-plate are for the attachment of cords or preferably of coiled springs for free swinging exercises.

(2) The standard Steinmann stirrup has been entirely re-designed. The bushes are much heavier and thumb-screws of stout gauge ensure efficient fixation. Each end of the stirrup wire is shaped like a crook so that it can be slipped on or off its bearing with a little pressure. Any rotation strain transmitted from the wire to the bushes and hence to the pin is negligible. The middle part of the stirrup, usually twisted into a circle, is now wavy, with a choice of five upward curves for suspension. The outer curves are particularly useful when external rotation of the limb has to be controlled. The whole stirrup can be taken apart into its three pieces or assembled again in a moment; this avoids all difficulty in threading a stirrup over the ends of a long pin.

The complete apparatus has been found of value in the treatment of various types of fractures of the femur, but especially for the first month after cup arthroplasty or Batchelor's pseudarthrosis operation, when both traction and free movements are required but external rotation must be avoided.

The President showed radiographs of a case of **Progressive Myositis Ossificans.**

Clinical Section

President—W. A. BOURNE, M.D.

[*November* 11, 1949]

Rheumatic Aortic Incompetence with Delayed Diastolic Murmurs on Auscultation

By AUBREY LEATHAM, M.R.C.P.
(*From the Cardiac Department of the London Hospital*)

AORTIC diastolic murmurs begin immediately after the second sound (Fig. 1). Wells, Rappaport and Sprague (1949) have shown that the crescendo of the murmur often occurs later on the phonocardiogram (Fig. 2). Recently we have seen two patients at the London Hospital in whom the aortic diastolic murmur seemed on auscultation to be separated from the second sound by a distinct gap; and caused difficulty in diagnosis. Phonocardiograms in each case show that diastolic vibrations begin at the second sound, but the main murmur comes later.

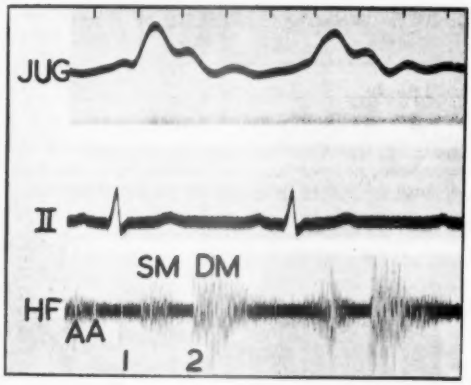


FIG. 1.—Aortic incompetence with typical diastolic murmur on auscultation. Synchronous jugular tracing, electrocardiogram lead II, and high frequency (HF) sound recording from the aortic area (AA). The aortic diastolic murmur begins immediately after the second sound.

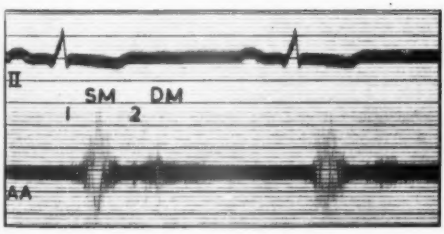


FIG. 2.—Aortic stenosis and incompetence with typical diastolic murmur on auscultation. On the phonocardiogram the diastolic murmur, though following the second sound, is maximal later.

Case I.—Mrs. F., aged 36, had chorea at the age of 7 and again at 9 years. The heart was first in question at the age of 16. Now she has slight palpitation but no other symptoms, not even breathlessness on exertion. The pulse is slightly collapsing in quality and the blood pressure is 140/60. External to the apex there are presystolic and mid-diastolic murmurs of mitral stenosis, but they are localized to a small area and only clearly heard after exertion. There is no systolic murmur. The outstanding physical sign is a loud diastolic murmur at the lower left sternal edge. The murmur is high pitched like any aortic diastolic murmur, but its remarkable feature is a gap between the second sound and the onset of this murmur; for this reason the patient was referred by Dr. William Evans for phonocardiography. A high-frequency (Leatham, 1949) sound recording from the lower left sternal edge (Fig. 3) confirms that the main aortic diastolic murmur is late and begins over 1/10 sec. after the second sound, but some vibrations, not enough to be audible, begin immediately after the second sound. That aortic valve disease is the main lesion is supported by finding left ventricular preponderance in the electrocardiogram and left ventricular enlargement on cardioscopy, with equivocal radiological evidence of mitral stenosis as the subsidiary lesion.

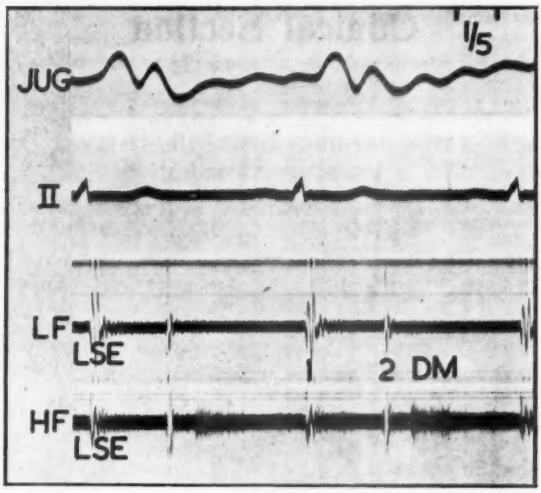


FIG. 3.

FIG. 3.—Aortic incompetence with delayed diastolic murmur on auscultation (Case I). A high frequency recording from the left sternal edge (LSE) shows that the main murmur begins over 1/10 sec. after the second sound, though some vibrations, not enough to be audible, begin immediately after the second sound. The murmur is too high pitched to be shown in the low frequency (LF) recording from the same area.

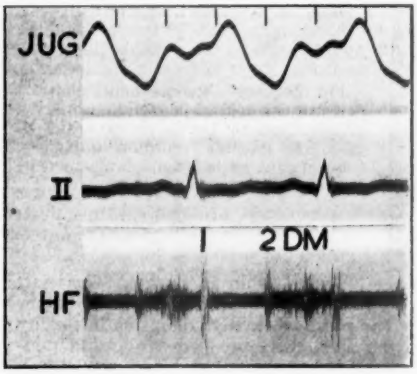


FIG. 4.

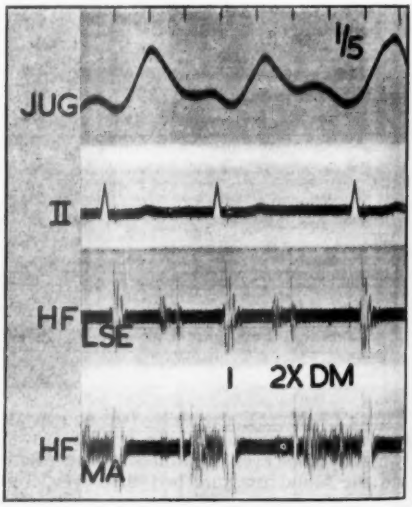


FIG. 5.

FIG. 4.—Aortic incompetence with delayed diastolic murmur on auscultation (Case II). A high-frequency recording from the left sternal edge shows that the main diastolic murmur is late though some vibrations begin immediately after the second sound.

FIG. 5.—The phonocardiogram of a patient with mitral stenosis for comparison with those of aortic incompetence. High-frequency recordings from the apex (MA) and synchronously from the left sternal edge (LSE) show the second sound, a gap, the opening snap (X) separated by a short interval from the mid-diastolic murmur of mitral stenosis. The vibrations immediately after the second sound are probably due to a slight degree of aortic incompetence.

Case II.—Miss C., aged 28, had rheumatic fever at the ages of 13, 18 and 20 years. Following the last attack she was told that her heart was affected. Now she has no symptoms. The pulse is moderately collapsing in quality and the blood pressure is 165/60. At the lower left sternal edge there is a loud high-pitched diastolic murmur separated from the second sound by a gap. The phonocardiogram (Fig. 4) confirms that the main diastolic murmur is late though some vibrations begin immediately after the second sound. The presence of aortic valve disease is supported by left ventricular preponderance in the electrocardiogram and slight left ventricular enlargement on cardioscopy. There is no clinical or radiological evidence of mitral valve disease.

The phonocardiogram (Fig. 5) of a man aged 43 with mitral stenosis is shown for comparison with the records of aortic incompetence and unusual diastolic murmurs. At the apex (MA) there is an obvious mid-diastolic murmur; here and at the lower left sternal edge (LSE) there is a loud sound (X) following the second sound, the so-called "opening snap" of the mitral valve. It precedes the mid-diastolic murmur by a short interval. Between the second sound and the "opening snap" are some vibrations which probably represent the early diastolic murmur of aortic incompetence which was just audible on auscultation.

In conclusion, it is well known that aortic diastolic murmurs begin immediately after the second sound but graphically this murmur may be shown to be maximal later. In rare cases the late crescendo may create the auscultatory impression that the murmur is separated from the second sound by a gap. This may cause difficulty in diagnosis though the murmur may be otherwise typical of aortic incompetence in its location and high pitch.

My thanks are due to Dr. William Evans for referring both cases to me.

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Constrictive Pericarditis and Mitral Stenosis.—FREDERIC JACKSON, M.R.C.P.

The patient, a male aged 52, had rheumatic fever three times in childhood. He had no known contact with tuberculosis. All his life he had been a little short of breath on exertion but had worked as a farmer until the age of 47.



FIG. 1.



FIG. 2.

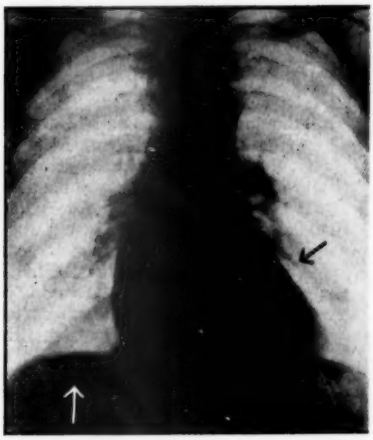


FIG. 3.

FIGS. 1 and 2.—Anterior and left oblique views. Slight enlargment of the heart. Calcium in the pericardium and in the dome of the right diaphragm.

FIG. 3.—Right oblique view. Left auricular impression on the barium-filled œsophagus.

In 1946 he was seen with symptoms of heart failure of two years' duration. His pulse (70–80 a minute) was irregular from auricular fibrillation; the venous pressure was raised (13 cm. of water); the liver was enlarged, but there was neither ascites nor œdema. A moderately loud systolic murmur was heard at the apex, but no diastolic murmur, and a third heart sound followed closely after the second sound.

On radiological examination the heart was slightly enlarged, calcium was seen in the pericardium (Figs. 1 and 2), and the left auricular impression on the barium-filled œsophagus was a little prominent (Fig. 3). In addition there was a plaque of calcium in the pleura over the right diaphragm (Figs. 1 and 2).

A diagnosis of mitral stenosis was considered but could not be proved. The venous distension and liver enlargement without other signs of failure in a man with moderately slow auricular fibrillation and clear triple rhythm suggested pericardial constriction. Calcium in the pericardium with minimal enlargement of the heart supported this view, and a diagnosis was made of constrictive pericarditis with probable rheumatic heart disease.

Pericardiectomy was performed by the late Mr. Tudor Edwards. The pericardium was thickened, densely fibrous and contained plaques of calcium; it was closely adherent to the heart, and it was stripped from both ventricles and the apex.

Since the operation the venous pressure has remained normal and the liver edge has receded, but symptomatic improvement has not been as favourable as expected. This may be due to additional mitral stenosis which can now be recognized by hearing a mid-diastolic murmur. The disappointing clinical improvement leads one to question the advisability of the operation in this case, despite the relief of the constriction and the lowering of the venous pressure.

Constrictive pericarditis is believed by many to be tuberculous in origin though evidence of the infection is frequently lacking. This case is likely to be an association of the effects of tuberculosis and rheumatic fever, two common diseases, existing together in the same patient. The difficulty remains, however, as to how far the symptoms must be ascribed to each.

Dr. A. Elkeles: Dr. Jackson's case is of special interest, since it shows that rheumatic fever can be an ætiological factor in the production of chronic adherent calcified pericarditis. I had the opportunity of investigating radiologically two cases of mitral stenosis with auricular fibrillation and signs of constrictive pericarditis. Oblique and lateral X-rays of the heart showed diffuse calcification of the pericardium. There was no evidence of tuberculosis. Mitral stenosis and tuberculosis exclude each other to some extent. In the past calcified opacities in the lungs sometimes met with in cases of mitral stenosis have been interpreted, probably wrongly, as evidence of pulmonary tuberculosis. In recent investigations Elkeles and Glynn (1946) have proved that some lesions can be due to intra-alveolar bone formations with no evidence of tuberculosis. Harkavy (1941) drew attention to the occurrence of constrictive pericarditis and even polyserositis in cases of severe vascular allergy with eosinophilia, in which the chief precipitating factor was bacterial allergy, resulting from chronic infection of the paranasal sinuses. In my opinion, the widely held view that tuberculosis is the most common ætiological factor in chronic adherent pericarditis has to be revised.

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Xanthomatosis Peritonei. ? Carcinoma of the Bronchus.—J. S. STAFFURTH, M.D., M.R.C.P. (for REGINALD HILTON, M.D.).

G. P., a retired police sergeant, aged 64.

1942: Skin lesions first noticed. W.R. ++.

1947: At an operation for right inguinal hernia free fluid was found in the peritoneal cavity. The peritoneum itself was thickened and white, and on section showed chronic inflammatory change with a large number of foam cells. Blood cholesterol 97 mg.%.

April 1949: A hard irreducible lump appeared at the site of the previous hernia. At operation this was found to be a yellow tumour at the apex of a hernial sac. Free fluid was present in the peritoneal cavity.

Since then he has lost weight, the ascites has become more troublesome and for three months he has complained of hoarseness of voice. There is only slight cough.

. Family history is not relevant.

On examination.—The patient is thin. Xanthomatous deposits are present in both axillæ, elbows and in the inguinal folds; also along the margins of the eyelids and in the inner canthus of both eyes. There is diminished air entry of the left side of the chest with impaired percussion at the left base; considerable ascites; palpable liver; large spleen.

Investigations.—X-ray of chest shows a mass at the left hilum. Screening shows a paralysed left diaphragm. Blood cholesterol 70 mg.%. W.R. negative. Plasma proteins 4·4 grammes% (albumin 2·5, globulin 1·9 grammes%). Bronchoscopy: Immobile left cord; bronchial tree normal.

He has just completed a course of radiotherapy to the left hilar region, but as yet there is no improvement in symptoms and only slight change in the radiological appearance.

POSTSCRIPT (14.12.49).—Dr. G. B. Dowling's report reads: "There are large patches of superficial xanthomatosis in the axillæ, in the elbows, on the upper eyelids, in the post-auricular folds and in the inguino-crural areas." He stated that he had not seen lesions like this in xanthomatosis before.

Biopsy report (Dr. J. Bamforth): "Small clumps of foam cells chiefly associated with blood vessels are present in the lower part of the dermis and in the subcutaneous tissue." Dr. Dowling has seen this section and he has no doubt that the lesions are due to xanthomatosis.—J. S. S.

Dr. F. Parkes Weber said that foam cells might abound in some chronic inflammatory conditions (for instance, xanthomatous salpingitis) as well as in certain neoplastic conditions, including so-called xanthosarcoma and osteoclastoma. (Compare F. P. Weber on "Xanthomatous formations in inflammatory tissue and true tumours" in *Modern Trends in Dermatology*, London, 1948, p. 311.) The present case showed a chronic thickening of the peritoneum containing foam-cells, which perhaps might be termed "xanthomatosis peritonei", but the condition in the thorax was more likely to be a malignant neoplasm of quite different nature. He (F. P. Weber) could find no evidence of any cutaneous xanthomatosis as far as his single inspection and the illumination permitted.

POSTSCRIPT (16.11.49).—In some respects the peritoneal condition should be compared with that in the case termed "intestinal lipodystrophy" by C. H. Whipple, 1907, *Johns Hopk. Hosp. Bull.*, **18**, 382.—F. P. W.

Dr. G. E. Vilvandré: I have no doubt that the chest condition is malignant. The paralysed left dome of the diaphragm and a paralysed left vocal cord support this diagnosis, and in my opinion the lateral view is in favour of a bronchial neoplasm.

Irradiation and Diathermy Necrosis Right Breast with Intractable Pain. Treated by Excision of Ulcer and Transference of Left Breast with Dermatome Graft to Secondary Defect.—PATRICK CLARKSON, M.B., B.S., F.R.C.S.

E. M. T., female, aged 68.

May 1945: Pain in left breast for past three months. B.P. 260/120. Coronary thrombosis 1943.

1945: Radium implant for carcinoma of breast.

1947: Irradiation. This was followed by intractable pain and necrosis over the site of the right breast. Alcohol injection in 1947. No relief.

20.7.48: Excision of neoplastic ulcer; Mr. Anthony Green and Mr. F. D. Saner using diathermy. Partial cover by free graft later (P. C.).

In view of the dense fibrosis of the whole of the chest wall surrounding the ulcer and the extensive necrosis of ribs and cartilage, it was felt that a free graft would not provide a stable cover. Equally, a posterolateral flap from the same side was considered uncertain as all this tissue had been extensively irradiated. A flap therefore had to come from the opposite side. The most adjacent tissue was the opposite breast. It was considered safer to do this breast transference in two stages.

30.12.48: Local excision of sloughs and superficial necrotic cartilage and bone. Delay of left breast flap (*see* Fig. 1).



FIG. 1.—Left breast "delayed". At same operation sequestrectomy and removal of sloughs from surface of radiation ulcer.



FIG. 2.—Post-operative result. Ulcer plus an area 6 in. across of scar tissue has been excised and the left breast swung over the defect with a dermatome graft to the secondary defect on the left.

15.1.49: Radical excision of scarred area including "clean ulcer" and 6 in. of fifth and sixth chondro-costal junctions. Defect of 6 in. diameter established. Transference of left breast over this raw area on right. Dermatome graft to secondary defect on left.

Healing complete three to four weeks later (Fig. 2). Complete relief of pain with increase in weight and appetite, and relief of insomnia.

Rheumatoid Arthritis Following Thyrotoxicosis.—FRANCIS BACH, D.M.

F. T. B., male, aged 30.

Previous history.—Whilst in the R.A.M.C. at the age of 20, he first noticed loss of weight, increased sweating and fatigue. Some protuberance of his eyes was then present. One year later he received a course of deep X-ray therapy at Leeds Infirmary for thyrotoxicosis. He was discharged from the Army in June 1942 and remained well until July 1943, when his symptoms returned, with frequent attacks of palpitation, and he was admitted to St. Bartholomew's Hospital. His basal metabolic rate was within normal limits but, in view of his symptoms, a partial thyroidectomy was carried out in October 1943. His general health improved and sweating diminished.

Within one month of his discharge from hospital, he developed an acute polyarthritis of the rheumatoid type, with a rapid onset of contractures and deformity and, within a year, he was completely crippled. He was transferred to Bath and treated with gold; his general weakness precluded hydrotherapy.

On admission to St. Stephen's Hospital, 1944, he was completely crippled, with advanced rheumatoid arthritis. There was marked flexion deformity with spasm of the muscles of the hip, knee and shoulder joints.

Blood count.—R.B.C. 4,190,000; Hb 71%; C.I. 0·8; W.B.C. 7,900 per c.mm. E.S.R. 80 mm. in 1 hr. (Westergren). Blood cholesterol and serum proteins normal.

There was no response to general medical treatment and, in December 1944, it was decided to perform a splenectomy. This was followed by marked improvement in his general health, relief of muscle spasm and the return of his sedimentation rate to the upper limits of the normal by April 1945.

During the next few years, a series of manipulations and reconstructive operations were carried out with the aim of making him fit to return to a sedentary occupation. In April 1949 he was transferred to Queen Mary's Hospital, Roehampton, to await the provision of a motor chair in order that he might return to his clerical employment.

This patient is shown to stimulate discussion on the relationship of the spleen, thyroid and adrenal cortex to rheumatoid arthritis, and to ask advice on: (*a*) the relationship of the thyroid and adrenal glands to rheumatoid arthritis, and (*b*) the role of the spleen in this disorder.

Comment.—In 1940 with Oswald Savage, I reported 3 patients under my care in whom splenectomy had been performed, and reviewed the literature on the subject (*Ann. rheum. Dis.*, 1940, **2**, 47).

In 1946, I presented at this Section a young woman in whom a rheumatoid type of arthritis had been quiescent following splenectomy (*Proc. R. Soc. Med.*, 1946, **39**, 306). I then suggested that rheumatoid arthritis was a psychosomatic syndrome in which metabolic and psychological factors appeared to play a more important role than did focal infection, and pointed out that in starvation, pregnancy and jaundice there is often a dramatic diminution in the severity of the symptoms but improvement was, unfortunately, only of short duration. I suggested that, in these conditions as well as that following splenectomy for acholuric jaundice there is a retention of cholesterol in the blood, and that cholesterol has been claimed as the mother substance of hormones, vitamins and carcinogenous substances. From the oxidation of certain side-chains of the cholesterol formula are derived: (*a*) the nucleus of bile salts, (*b*) testosterone, (*c*) steroids of the adrenal cortex, (*d*) stilbœstrol, all substances which are used by clinicians in the treatment of rheumatoid arthritis.

Last year Compound E, now known as Cortisone, and A.C.T.H. (adrenocorticotrophic hormone) attracted much attention following the magnificent work of Kendall and Hench of the Mayo Clinic and Thorn of Boston.

This year, at the Mayo Clinic, I was privileged to see the dramatic clinical response to injections of Compound E in rheumatoid arthritis. This demonstrated the "clinical reversibility" of this "potentially reversible disease" (Hench). Unfortunately, the clinical response occurs only if massive doses (much above physiological levels) are given (100 mg. daily parenterally).

Cortisone is not and, in my opinion, will not be the *treatment* for rheumatoid arthritis. It is someone else in the endocrine orchestra who is the villain. The fault may lie in a man's philosophy of life, his psychological reactions, his hypothalamus, pituitary, adrenals or in his spleen. A psychological approach by a general physician plays an important role in prevention and early treatment. Surgical intervention must necessarily be a crude method of treatment.

The recent papers of Professor Means and others (*Lancet*, 1949 (ii), 543) have pointed out the close association of the thyrotrophic and the adrenotrophic hormones. In thyrotoxicosis, the secretion of both is increased, in myxœdema diminished.

In this patient, thyroidectomy was followed immediately by an acute rheumatoid arthritis. Was this due to a sudden cutting down of the adrenocortical hormone, thus producing

the clinical picture of rheumatoid arthritis? Was this "potentially reversible disease" reversed by removal of the patient's spleen?

Mr. T. Levitt stressed that although rheumatoid arthritis did not accompany thyrotoxicosis frequently, patients with joint pains had shown some improvement after thyroidectomy. The case, however, presented important features showing that the exophthalmos was of a type which one would classify as "malignant", that is, it would not improve after thyroidectomy.

At the Thyroid Clinic, New End Hospital, cases of prominent eyeballs were classified as follows: (1) *Pseudo-exophthalmos*, which was essentially a condition of lid-lag and would usually be cured by thyroidectomy;

(2) *True exophthalmos*, consisting of two types: (*a*) The *benign* group. Here the protruding eyeballs were neither tense nor tender and could be pushed back into the orbit quite easily. This condition was due to an excess of retro-orbital fat. It had been cured successfully by an intra-orbital operation, originated and practised by Mr. J. E. Piercy, in which this excess of indurated fat was excised. (*b*) The "*malignant*" group presented tense, tender and protuberant eyeballs simulating an elastic ball which could not be pushed back into the orbit. There was no excess of indurated fat. An operation of the Naffziger type was required where part of the bony confines of the orbit was removed.

Intraspinal Neurofibroma and ? Neurofibroma of Neck.—J. F. BUCHAN, M.B., M.R.C.P. (for ERNEST FLETCHER, M.D.).

M. M., male, aged 43. A dyer and cleaner.

Admitted 27.6.49 to Royal Free Hospital, Unit of Rheumatology, complaining of pain in the right hip and down the outer side of the right thigh and in the right knee.

The pain originally came on suddenly in 1937, after defæcation. Treated with various mixtures and physiotherapy without relief. Eighteen months ago pain became much worse and the patient lost weight (9·6 kilos) and much sleep. Treated with intramuscular injections of benzyl salicylate and later by the application of a plaster jacket, in each case without relief of pain.

There was nothing relevant in the past or family history.

On admission.—General condition good. Hard lump deep to L. sternocleidomastoid muscle. Limitation of all movements in the dorsal and lumbar spine and a gradual kyphoscoliosis. Spasm of erectores spinæ. Weakness of flexors of R. hip. Wasting of R. thigh. R. knee-jerk absent, left very sluggish. Both ankle-jerks present and equal. Plantar responses flexor. Diminution in sensation in the distribution of L.3. Lumbar puncture: Froin's syndrome; initial pressure 195 mm. H_2O, with complete spinal block.



FIG. 1.—X-ray of lumbar spine showing changes in the twelfth thoracic and first lumbar vertebræ brought about by an intraspinal neurofibroma.

M. M. was transferred to the Atkinson Morley Hospital on 25.7.49. X-rays of the lumbar spine, A-P views, showed that the peduncles of the twelfth thoracic and of the first lumbar vertebræ were abnormally widely separated. Lateral views (Fig. 1) showed erosions of the pedicles of the same vertebræ, on the left side, and also of the posterior aspects of the bodies. The left D.12–L.1 vertebral foramen was much enlarged.

Mr. Valentine Logue found a very large neurofibroma arising probably from the first and second right lumbar nerves and extending out through the intervertebral foramen. Owing to its large size the intraspinal part of the tumour was removed piecemeal. The nerve roots of the cauda equina had been pushed over to the left and were much flattened, as was the conus medullaris, by the tumour.

Pain disappeared post-operatively but the weakness of the right quadriceps has not improved much.

This is the second case seen during the last two and a half years at the Royal Free Hospital, Unit of Rheumatology. During this time 596 cases have been admitted.

Camp and Adson (1931) and Brailsford (1948) clearly describe the radiological changes found in a case of this kind.

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Mediastinal Abscess Following Removal of Foreign Body from Œsophagus with Subsequent Pharyngo-œsophageal Diverticulum.—H. WOLFSOHN, M.D., M.R.C.P.

Mrs. L. W., aged 37.

Ingestion of foreign body.—Admitted to St. Mary Abbots Hospital on 11.2.49 with severe discomfort after a fish meal the previous evening. Radiography revealed a metal wire at the upper end of the œsophagus which was removed by œsophagoscopy (Mr. S. Beards). After this she had four attacks of fever at home which subsided in 3 to 7 days.

Mediastinitis and abscess formation.—On 4.5.49 she was readmitted in a very ill condition complaining of a dry irritating cough, breathlessness, substernal pain and hoarseness of voice. Temperature 104·4°. X-ray (Fig. 1) showed a rounded opacity in the right lower



FIG. 1.—Central rounded opacity in the right upper chest. Mediastinal abscess.



FIG. 2.—Pharyngo-œsophageal diverticulum. The mediastinal abscess is no longer seen.

paratracheal zone. This soon spread into the right upper lung fields, then diminished in size and had practically disappeared six weeks later. Non-hæmolytic streptococci, micrococci, pneumococci, *Staph. albus* and diphtheroids were grown from the sputum but no tubercle bacilli. A barium swallow on 20.5.49 demonstrated slight cardiospasm and doubtful irregular indentation along the posterior pharyngeal wall opposite D3 to D5.

Treatment.—Procaine penicillin in oil 300,000 units daily with penicillin inhalations from 4.5.49 to 5.6.49. She was then symptomatically improved although still pyrexial (98°–100° F.). Streptomycin (0·5 gramme eight-hourly) was given from 5.6.49 until 13.6.49, after which her temperature was normal with an occasional rise to 98·6° F.

7.7.49: Discharged to a convalescent home. E.S.R. was still 24 mm./hour, but she was feeling well and gaining weight.

Œsophageal diverticulum.—After returning from the convalescent home on 28.7.49 she complained of an odd clicking sound when swallowing certain solids. There was a tendency to regurgitation of undigested food shortly after swallowing.

Barium swallow examinations (15.9.49 and 25.10.49) revealed a pouch (Fig. 2) arising from the posterior wall of the hypopharynx at the level of C6 extending to D1.

Comment.—The diverticulum arises in the classical position in the hypopharynx. It is of very recent onset as (*a*) symptoms of dysphagia, regurgitation of food and the clicking sound only occurred in July, (*b*) a barium swallow in May had failed to show the presence of a pouch, and (*c*) on œsophagoscopy in February no such pouch was seen. The trauma produced by the foreign body and the subsequent local inflammation which also led to mediastinitis are considered to have further damaged the potentially weak "pharyngeal dimple" between the oblique and cricopharyngeal fibres of the inferior constrictor muscle. This produced herniation of the mucosa and submucosa and, in consequence, a typical pulsion diverticulum.

POSTSCRIPT.—Treatment by surgical removal has been successful. H. W.

Section of Laryngology

President—R. D. Owen, B.Sc., F.R.C.S.

[*December* 2, 1949]

DISCUSSION ON THE TONSIL AND ADENOID PROBLEM

R. S. Illingworth (Professor of Child Health, The University of Sheffield): The remarkable antipathy possessed by many for the tonsil is exemplified by the work of Denzer and Felshin (1943). They examined 1,000 11-year-old New York school children and found that 610 had had their tonsils removed. The remaining 390 were referred to 20 school medical officers, and all but 65 were advised to have the tonsils taken out. Glover (1938, 1944, 1948) has drawn attention to the great frequency of the operation in this country and to the remarkable variation in its incidence from town to town. Glover (1948), Colins and Sydenstricker (1927), Kaiser (1930), Paton (1928, 1943), pointed out that the operation is performed much more frequently in the rich than in the poor. Whereas in elementary schools in this country about 20% of children have had the operation before the age of 14, 83% of new entrants to Eton in 1938 had had the tonsils out.

Difficulties in the Interpretation of Published Work

(1) *Failure to correlate bacteriological study of the tonsils with the disease for which they are removed.*—It would seem logical that if tonsils are to be removed as part of the treatment of acute nephritis, rheumatic fever, or other condition related to the hæmolytic streptococcus, only those tonsils should be removed in which there is evidence of that infection. Almost all papers fail to give such information, the writer's included (Illingworth, 1939*b*). Admittedly, the presence of hæmolytic streptococci in a throat swab does not prove that those organisms are the cause of the disease or represent anything more than the carrier state, but their presence would at least be a guide to rational treatment. It is possible, but unproved, that the removal of tonsils, in which there is a persistent hæmolytic streptococcal infection, might benefit the course of nephritis or rheumatic fever. Inclusion in statistical studies of the effect of operation in children with no such infection is very likely to obscure good results, if any, from an operation done for proper indications.

It is a well-recognized fact that a considerable proportion of cases of acute tonsillitis are due neither to the hæmolytic streptococcus nor to other known organisms, and are probably virus in origin. The commission on Acute Respiratory Disease (1946) in a three-year study of exudative tonsillitis and pharyngitis at Fort Bragg, found that only 25% showed satisfactory bacteriological evidence of streptococcal infection. In children suffering from recurrent tonsillitis the effect of the removal of those tonsils which were infected with the hæmolytic streptococcus might well be very different from that of removing tonsils in which there is no such infection. We have no information on that point.

There have been a few bacteriological studies of tonsils removed at operation, but little correlation between these findings and the symptoms of the patient. Caylor and Dick (1922) attempted to correlate a quantitative bacterial count in the tonsils removed at operation and the incidence of rheumatic fever. They found that clinical improvement occurred when heavily infected remnants were removed.

(2) *Unsatisfactory evidence of completeness of the operation.*—Very few papers on tonsillectomy give satisfactory evidence that the operation has been complete. Opinions as to the frequency of remnants differ considerably. Paton (1943) put the figure at "well over a third".

Gordon (1947) found remnants in 42·4% of 1,000 children who had had the operation. McLaggan (1930) found remnants in 49%, Clark (1913) in 42%, Rhoads and Dick (1928) in 73%, Campbell (1939) in 77·3%, Meyer (1946) said "I believe that complete tonsillectomies are performed rarely". It is possible that some of these so-called remnants represent merely compensatory hypertrophy of remaining lymphoid tissue. It is certainly unreasonable, in a condition such as nephritis or rheumatic fever, to compare the effect of tonsillectomy, when a remnant is left which may grow as large as the original tonsils with the effect of leaving the tonsils intact. The possible good results of the operation are obscured by poor results arising from poor operative technique. Rhoads and Dick (1928), Campbell and Warner (1930), and Meyer (1946) have all discussed the good results achieved by removing infected tonsil remnants. Caylor and Dick (1922) found that one tonsillar remnant examined by them contained more organisms than all other tonsils investigated. Campbell (1939) considered that such remnants are often a greater menace to a patient, both locally and generally, than the original tonsils.

The compensatory hypertrophy of remaining lymphoid tissue after the operation for tonsils and adenoids has often been discussed (e.g. Bordley, 1947; Crowe, 1944). Crowe stated that adenoids recur in 75% of children in whom the operation is done before puberty. It is uncertain whether this compensatory hypertrophy of lymphoid tissue is of value to the patient for the development of immunity, or of disadvantage to the patient as a nidus of infection. The literature does not compare the effect of medical treatment, in such conditions as rheumatic fever, with a really complete operation.

(3) *Persistence of infection.*—With very few exceptions the literature does not tell us whether the infection for which the operation has been performed has been removed or not. It is well known that a streptococcal infection commonly persists after the operation. If it does persist one can hardly expect the operation to prove an effective therapeutic measure. Longcope and co-workers (1935) stressed the importance of this persistence of infection after operation for nephritis. Allen and Baylor (1938) found that exacerbations of rheumatic fever were much more frequent in those children in whom infection persisted after tonsillectomy than in those in whom the infection was cured by operation.

(4) *Inadequacy of treatment.*—Bound up with the topics discussed above is the fact that in any clinical study, in which comparison is made between two lines of treatment, it is essential that in each case the treatment should be really adequate and thorough. Most of the literature on tonsillectomy merely compares the effect of the removal of the tonsils with that of leaving them intact. It does not compare the effect of proper medical treatment, including chemotherapy, with the effect of *complete* removal of tonsils and adenoids, in which there are no remnants, and in which any residual infection is properly treated by chemotherapy and other methods. Too often the throat is forgotten when once the tonsils have been removed. Once more, the good results of the operation, when properly performed for adequate reasons, and with proper after-care, are obscured by the bad results of inefficient techniques and inadequate post-operative treatment.

The writer is unaware of any study which compares the effect of tonsillectomy, for such conditions as recurrent tonsillitis, nephritis or rheumatic fever, with prophylactic chemotherapy designed to prevent streptococcal infection.

(5) *The combined or single operation.*—The literature leaves us very much in the dark as to whether the tonsils and adenoids should be removed in various conditions, or whether it is sufficient for only one or the other to be removed. Most of the literature concerns the combined operation.

(6) *The timing of the operation.*—This may be of importance in such diseases as nephritis, but it is hardly mentioned in the papers on the subject. It is possible that the operation would prove valuable if done early—but there is no evidence to that effect. Rudebeck (1946) found that the operation was of no value in nephritis, however early it was performed. There is a natural tendency to perform the operation when the disease has failed to respond to all other measures, or is already hopeless. There is evidence that the operation fails in those circumstances, but for reasons stated the investigations have been inadequate and do not prove that operation is never of value in the condition.

(7) *Methods of controlling.*—The method of controlling used in many papers has been unsatisfactory. Many papers fail to take the factor of age into account. A child is older after the operation than before it and the fact that he improves after the operation is no proof that the improvement is due to the operation. Most children develop a natural immunity to upper respiratory tract infections at the age of 6 or 7—the very age at which the peak incidence of tonsillectomy is reached. All comparisons of morbidity rates must be made in children of the same age group. Social factors, racial and geographical factors have to be taken into account. There is a higher incidence of streptococcal infections in some places than in others. Too often those factors are ignored in papers on tonsillectomy.

Many papers compare the health of those who have had the tonsils removed with that of children with intact tonsils. Many of these studies depend entirely on the history given by the mother. This is very apt to be fallacious. A mother who was anxious to have the operation performed is very likely to express satisfaction at the results of the operation and say that the child is better. Studies based on doctors' reports sent to school to explain a child's absence are somewhat more reliable. This sort of study helps little, however, for it is clear that those who have had the operation are likely to have had it for some reason, however bad that reason, and that there will be a higher incidence of colds, otitis and other infections in those submitted to operation than in controls. It is possible that those submitted to operation might have been worse if not operated on. Kaiser's investigation (1930), though one of the most careful, is not entirely satisfactory. He conducted a ten-year follow-up of 4,400 children who had been advised to have the operation. Half those children submitted to the operation, while the other half for various reasons were not operated upon. Subtle differences in the two groups reduce the value of the investigation. In the group of children who did not have the operation the parents may have been less co-operative and less intelligent, and so given a less accurate follow-up history of infections. There are many other difficulties in published work which make the interpretation of the results particularly difficult.

(8) *The duration of the follow-up.*—This has been inadequate in most papers. Kaiser showed how the incidence of colds and otitis media was less in the operated group for the first three years after the operation, but became greater thereafter than in the control group. It is possible that the operation caused a postponement of the age at which immunity to upper respiratory tract infections is normally developed.

(9) *Errors in diagnosis.*—Inaccuracy of diagnosis has led to many unnecessary operations. Once more the poor results of the operation done for improper indications obscure the good results of the operation done for proper reasons.

(*a*) *Sinus infections*: It seems certain that many of the symptoms for which tonsils and adenoids are removed are, in reality, due to infection of the nasal sinuses. Most papers make no mention of this. Crooks and Signy (1936) found infected sinuses in 24 out of 100 children at the time of tonsillectomy. 15 of the 100 children investigated had a chronic sinus infection. Griffiths (1937), Dean (1934), Selkirk and Mitchell (1931), Walker (1947), and others all emphasized the frequency of sinus infections in children sent up for tonsillectomy. Crooks (1938) found that only 9 out of 24 children with sinus infections were improved by tonsillectomy.

(*b*) *Adenoid facies*: This may be due to any nasal obstruction, and is not due merely to adenoids.

(*c*) *Mouth-breathing*: This may be due to several causes other than adenoids. It may be due to a habit, nasal obstruction, malocclusion or mental defect. Crooks (1938) said that there was mouth-breathing in 62% of his cases of chronic sinus infection. Epstein (1937) emphasized the frequent failure of adenoidectomy for the relief of mouth-breathing in children under the age of 6 years.

(*d*) *Colds*: So-called colds are often an allergic rhinitis or sinus infection.

(*e*) *Postnasal discharge*: This is often due to a sinus infection.

(*f*) *Growing pains*: Pains in the thighs rather than joints, are often wrongly called rheumatic fever. They do not respond to tonsillectomy, and, as far as is known, bear no relationship to the hæmolytic streptococcus.

(*g*) *Cervical adenitis.*—This is often due to dental caries, septic places on the face and scalp, and pediculosis capitis.

Other Difficulties Regarding Indications for Operation

(1) *Doubt about the function of the tonsil.*—It is generally thought that the function of the tonsil is that of immunity production. Most children acquire relative immunity to upper respiratory tract infections at the age of 6 or 7, and thereafter the tonsil decreases in size. It is possible that the regeneration of lymphoid tissue which follows the removal of tonsils and adenoids is designed by nature to help to produce that immunity. For this reason the complete destruction of lymphoid tissue by irradiation may or may not be altogether advisable.

Unfortunately we do not know at what stage the tonsil becomes more of danger than of value to its owner: there is no laboratory test which helps us to decide the question.

(2) *Focal sepsis.*—The problem has been adequately discussed by Reimann and Havens (1940) and others. We can certainly say that the theory of focal sepsis has largely fallen into disrepute, possibly for the same reason as the operation for the removal of tonsils—the great dilution of good results of treatment for proper indications with the bad results of random and unnecessary treatment.

(3) *Cervical adenitis.*—Many papers deal with the incidence of cervical adenitis before and after operation on the tonsils, and compare the incidence in children who have intact tonsils with that of children who have had them out. Most of these papers ignore the other common causes of cervical adenitis, mentioned above, and most make no attempt to define what is meant by cervical adenitis. What many would think normal others would think abnormal. Some define it as an adenitis which is visible. Few distinguish the non-suppurative from the suppurative form. Few papers, in fact, give us much help in assessing the value of the operation for the condition.

There seems little doubt that the fear of cervical adenitis is an exaggerated one. At one time it was thought that infected tonsils were the portal of entry for the tubercle bacillus. There is no evidence to this effect. It seems likely that many examples of tuberculosis of cervical lymph nodes, in adults at least, are due to infection via the blood stream, or infected sputum. Newhart and co-workers (1934) found that the tonsils of 48 out of 100 adults with pulmonary tuberculosis contained tuberculous foci, and Schlittler (1938) thought that most cases of tuberculosis of the tonsils in adults were due to infection from the lungs. The literature was reviewed by Rather (1943). We know that the tubercle bacillus can be recovered from the stomach washings in the great majority of children with primary lung tuberculosis, the organism having reached the stomach after being swallowed. We do not know how many cases of tuberculous cervical adenitis in children are of bovine and how many of human origin: but it is certainly advisable to take an X-ray of chest in all cases of tuberculous adenitis in children and to type tubercle bacilli which are recovered from glands which have broken down. It would not seem reasonable to perform a tonsillectomy for tuberculosis of the tonsils of human and therefore secondary origin.

In non-tuberculous cervical adenitis, as long as suppuration does not occur, there is no need to fear that the adenitis will harm the child. Enlarged nodes of this nature worry the mother, but not the child. Selkirk and Mitchell (1931) in their careful investigation found no evidence that the incidence of suppurative cervical adenitis is in any way reduced by the operation.

The extremely low incidence of cervical adenitis in the Basque school children who came to this country as refugees was noted by Ellis and Russell (1937): less than 2% of these children had had the tonsils removed.

(4) *Sore throat and tonsillitis.*—Some of the difficulties in the evaluation of published work on the subject have already been mentioned. Most papers ignore the difference between a sore throat at the commencement of a cold and a true tonsillitis. Most papers necessarily rely completely on the mother's history as to the frequency of tonsillitis. This history is notoriously inaccurate. The mother and father often disagree as to how often a child has tonsillitis. The finding of a follicular tonsillitis of which the parents are quite unaware and of which the child has not complained is commonplace. On the other hand a child may complain of a sore throat when inspection reveals nothing abnormal. Most papers on the effect of tonsillectomy on recurrent tonsillitis do not take these difficulties into account. It need hardly be added that true tonsillitis certainly should be rarer after the operation than before, just as appendicitis should be rarer after appendicectomy.

Another difficulty is that while many papers discuss the effect of the operation on the frequency of colds and sore throats, they do not discuss the effect on their severity. It might well be that careful investigation would show that while the frequency of colds is not affected by tonsillectomy, their severity is reduced. There is no evidence of this at present.

(5) *Nephritis.*—It is possible that once acute nephritis has developed the disease pursues its course irrespective of the removal of the source of infection. Addis (1931) inclined to this view, and quoted the experiment of E. C. Dickson, who caused acute nephritis in rabbits and guinea-pigs by giving them one injection of a uranium salt. The inflammatory reaction set up persisted long after all possible traces of the uranium had disappeared, chronic nephritis resulting. It would seem reasonable to suppose, however, that the prevention of exacerbations is desirable, and we know that exacerbations often follow a hæmolytic streptococcal infection. Such infections might well be prevented by prophylactic chemotherapy, as they are in rheumatic subjects, and there is no evidence that tonsillectomy will achieve more than prophylactic chemotherapy. If this failed to prevent infections, tonsillectomy would have to be considered, but the danger of tonsillectomy is the frequency with which it causes exacerbations of the nephritis. The writer (Illingworth, 1939*b*) found that the operation caused an exacerbation in 28 out of 119 nephritic children (24%) submitted to the operation, in one case causing death. It seems reasonable to suppose that such exacerbations are harmful to the child, for it is likely that they lead to a further destruction of kidney tissue. It would be interesting to determine whether chemotherapy or antihistamine drugs as a cover to tonsillectomy would prevent these exacerbations. In the present state of our knowledge one has to balance the risk of an exacerbation with the possible advantage of the operation. The trouble is that we do not know whether the complete removal of

tonsils, in which a hæmolytic streptococcal infection has been found, will do anything to cure the disease. We can certainly say that, as yet, there is no evidence that tonsillectomy has proved to be of any value in nephritis.

Much the same argument applies to rheumatic fever.

(6) *Complications of the operation.*—Complications following the operation are relatively infrequent, considering the enormous numbers of tonsillectomies, but far from rare. They tend to be seen much more by the physician than by the Ear, Nose and Throat Specialist. The Registrar-General's Returns (Glover, 1938) show at least 85 deaths each year from the operation under the age of 15. It is thought that this is an underestimate of the true position, because deaths are liable to be entered under such diagnoses as pneumonia, whereas really they are due to the operation. No purpose would be served by enumerating the various complications. The columns of the "Index Medicus" list numerous articles on the subject of complications of tonsillectomy, affecting almost every tissue in the body. Many of these complications are due, no doubt, to the bacteriæmia which so frequently follows the operation. Elliott (1939) found a bacteriæmia in 38 out of 100 children a few minutes after the operation. The organisms found included *Streptococcus pyogenes*, *Streptococcus viridans*, *Streptococcus pneumoniæ*, *Hæmophilus influenzæ*, *staphylococci* and *corynebacterium*.

There have been numerous articles concerning the danger of poliomyelitis after the operation. The evidence of that danger appears to be very strong. Aycock (quoted by Burnet, 1946) went so far as to say that the only known prophylactic measure to adopt in an outbreak of poliomyelitis is to stop all operations on tonsils and adenoids. The American National Foundation for Infantile Paralysis advised that no operation on the nose and throat should be performed during an epidemic of poliomyelitis (Editorial, *J. Pediatrics*, 1949). Magnus and Melnick (1948) showed that certain types of monkey investigated by them were rendered very much more susceptible to experimental poliomyelitis by tonsillectomy. Anderson (1945) compared the incidence of poliomyelitis following tonsillectomy before, during and after an epidemic of that infection. Before the epidemic began the poliomyelitis : tonsillectomy ratio was 0·7 : 1,000; at the height of the epidemic it was 25·5 : 1,000. Fischer and Marks (1941), Aycock (1942), and others noted the same connexion. Anderson (1945) showed that in Utah in 1943, 43% of cases of bulbar poliomyelitis were preceded by a tonsillectomy within thirty days of the onset. The incidence of poliomyelitis in those who had recently had the operation was 2·6 times more than that of the rest of the child population, while the incidence of bulbar poliomyelitis was 16 times greater than that of the rest of the child population. Cunning's evidence (1948) to the contrary, based on a questionnaire, is fallacious, because by that time the operation was not being performed in areas where the infection was prevalent.

Another striking and disturbing fact is the frequency with which the operation causes in some children a disease which, in others, it is intended to cure, or is followed by an increased frequency of that disease. Many have commented upon the frequency with which sinus infection follows the operation (Helmholz, 1930; Selkirk and Mitchell, 1931; Walker, 1947; Griffiths, 1937). The same workers found that infection of the sinuses was commoner in those who had had a tonsillectomy than in those whose tonsils were intact. The occurrence of otitis media after the operation is well known.

Kaiser (1948) found that although colds and otitis media occurred less frequently in the children who had a tonsillectomy, in the first three years after the operation, than in controls whose tonsils were intact, they occurred more frequently than in controls in the remaining part of the ten-year follow-up period. The writer (Illingworth, 1939*a*) in an investigation of 300 children with very frequent colds (averaging one per month) in the Outpatient Department of the Hospital for Sick Children, Great Ormond Street, found that the third commonest factor from which the colds originated was the operation on tonsils and adenoids. Many other workers have found a greater incidence of infections of the upper respiratory tract in those who have had the tonsils removed than in those whose tonsils are intact (Paton, 1928, 1943; Epstein, 1937; Selkirk and Mitchell, 1931; Forsythe, 1928; Glover and Wilson, 1932; Cunningham, 1931). Some of the difficulties, however, of assessing such studies have been discussed above.

In an investigation of nephritis in children (Illingworth, 1939*b*), the writer found that 18 (5%) of 365 cases of nephritis immediately followed, and were therefore presumably initiated by the operation. As already stated, the operation during the course of the nephritis caused an exacerbation in 28 out of 119 children (24%).

The psychological effect of the operation was discussed by Levy (1945). Night terrors were the characteristic response in children under 3, and negativism and fears of the dark, or of strange men, in children over 4. He thought that these responses were due largely to separation from the mother, and to the difficulty of explaining to the child what was going to happen to him.

Much more could be said about the complications of tonsillectomy, which are familiar to all physicians. Some of these are so serious that it behoves everyone to bear them in mind when considering the advisability of performing the operation in the presence of uncertain indications. The worst of these—death under the anæsthetic or from post-operative complication, is a terrible disaster which a man who has caused the operation to be performed without adequate indication, should never forget for the rest of his life. Most of us have seen such a death in children on whom the operation was done without any adequate reason.

False Indications and Contra-indications

(1) *The appearance of the tonsil.*—The most valuable contribution to the tonsil and adenoid problem in recent years is the work of Epstein (1937) at the Children's Memorial Hospital, Chicago. He attempted to correlate the careful observations of the physicians and throat surgeons in 152 children with the histological findings. He was unable to find any connexion between the severity of the symptoms and the degree of infection revealed by histology. "Some well-nourished children with no complaints save mouth-breathing had tonsils riddled with abscesses and sealed off by scar tissue. On the other hand some of the children complaining of almost constant sore throats had almost normal tonsils on histology." There was no relation between the size of the tonsil and the success of the operation in relief of symptoms. It was impossible to relate pathological evidence of infection with a history of preceding sore throats or other infections of the upper respiratory tract, neither could it be related to the prognosis. There was no connexion between redness of the anterior pillars and the degree of infection found. In some badly infected tonsils the anterior pillars were pale: some children had reddening of the anterior pillars, while their tonsils proved to be normal. He admitted that the tonsil with crypts, especially when much epithelial debris can be expressed, is usually infected. He concluded: "The physician does not know an infected tonsil when he sees one. There is nothing to lead one to feel that the appearance of the tonsils should ever influence one's judgment on the advisability of removing them. In children at least it would have a salubrious effect on the physician's attitude if he abandoned the diseased and hypertrophied tonsils and adenoids and substituted frequent sore throats or whatever the complaint or indication is. Whether tonsils were buried, cryptic, smooth, large or small bore no relation to the preoperative symptoms or the degree of success of the operation."

Many others feel that the appearance of the tonsil should not influence one's decision concerning the desirability of its removal (e.g. Denzer and Felshin, 1943; Brennemann, 1925; Dean, 1934). Most will agree that the mere size of the tonsil is no indication for the operation, except in the very rare cases in which the tonsils are so enormous that they may cause obstruction of respiration. It is normal for tonsils to enlarge at the age of 4 to 6, when immunity to infection is developing. There is some evidence of a connexion between the size of the tonsil and body build (Neuber, 1932), the large child tending to have larger tonsils than the smaller child. It is well recognized that large tonsils are not necessarily the most heavily infected ones. Caylor and Dick (1922) showed that the tonsils with the largest bacterial count per unit were the relatively small ones with chronic inflammatory changes.

Others think that the ability to express pus from the tonsil is a valuable indication for operation. More often than not, however, it is not pus which is expressed, but epithelial debris. The expression of either is often prevented by obstructing fibrous tissue.

It may be added that there is little agreement among pathologists as to what are the criteria of infection in the tonsil (Epstein, 1937; Wilkinson, 1929). Jackson and Coates (1929) concluded that: "Abscesses and abscessed crypts are present in varying numbers and sizes in all of the laryngopharyngeal lymphoid structures in the vast majority of human subjects beyond infancy—in other words a practically universal condition."

(2) *The recommendation of all and sundry.*—The decision as to the removal of tonsils should not rest with the school nurse, the mother, the father, aunt, neighbour or other lay person. Neither should the General Practitioner make the decision. He may know a lot about the child, but the decision must rest with the specialist. Neither should the pædiatrician push the throat specialist into removing the tonsils: rather he should state his opinion and ask for the opinion of his surgical colleague. No pædiatrician really respects the throat specialist who never has an opinion, who will not stand by his convictions, and who always does what he is asked to do for fear of causing offence. Some ear, nose and throat specialists have allowed themselves to become mere technicians, and to degenerate to the level of the fourth class general surgeon who first sees the acute abdomen on the operating table, instead of being consultants whose opinion is sought and respected, because it is known that they will give a carefully considered honest opinion after a full and thorough examination of the patient.

Some surgeons forget to put the child first. The child matters a very great deal more than the wishes of the doctor, nurse, mother or father. It is the child who suffers the discomfort of the operation and who may have to suffer complications of the operation. If a proper unhurried consultation is given in the out-patient department, and the problem is fully discussed with the parents, and their questions and fears are properly answered, it will be found that very few parents still want the operation to be performed when the consultant advises against it. No amount of insistence by the doctor or anyone else should ever make a surgeon perform an unnecessary operation on a patient.

(3) *Age.*—Tonsils should practically never be removed before the age of 4, and rarely before the age of 5 or 6. Adenoids should be removed for proper indications at any age.

(4) *General diseases.*—In the present state of our knowledge there is no justification for removing tonsils for any general disease unless they are producing local symptoms. They should not be removed for frequent colds, upper respiratory tract infections, or allergic conditions.

(5) *Absence of symptoms.*—They should never be removed in a child who is free from symptoms.

Suggested Indications

(1) The operation should only be recommended by a physician or surgeon if he would have it done on himself, under the same circumstances, or on his own child, due regard being paid to the possible risks of the operation.

(2) Tonsils should be removed on account of frequent tonsillitis with fever—three or four attacks a year.

(3) Tonsils should probably be removed after a peritonsillar abscess.

(4) Tonsils should be removed in the very rare case in which they are so large that they cause obstruction to respiration.

(5) Tonsils should probably be removed in diphtheria carriers in whom other treatment has failed.

(6) Adenoids should be removed when they are causing obstruction to the Eustachian tube, or are causing mouth-breathing, or are preventing the drainage of secretions, at whatever age the trouble occurs.

The writer cannot express an opinion as to whether the tonsils should be removed at the same time as the adenoids, or whether adenoids should necessarily be removed when tonsillectomy is performed.

Final Suggestions

If the operation is to be performed, it is suggested that :

(1) It should be done at a suitable time of the year.

(2) It should only be done when the child is an in-patient, never as an out-patient.

(3) The child, if old enough, should be told about the sensations he is going to experience.

(4) He should be given full premedication, so that he does not experience the unpleasantness and frightening experience of an anæsthetic.

(5) The operation should be done by dissection.

(6) The child should have proper convalescent treatment.

(7) He should be properly followed up so as to ensure that the infection for which the operation was performed has been eliminated.

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THE TONSIL PROBLEM (*Abridged*)

History.—Removal of the tonsils was mentioned first in the literature by Celsus [1] in the year A.D. 10. He speaks with some familiarity of the operation and describes complete removal. In more modern times Physick [2] of Philadelphia was the first to stress the importance of complete removal of the tonsils and he introduced the first tonsillotome or guillotine. As Scott Stevenson [3] has said the rise in incidence of this operation has been one of the major phenomena of twentieth century surgery. The realization of some of the benefits to be obtained from some of the operations in suitable cases led to a wave of over-enthusiasm for operation. This is an easy operation—to do badly ; and therefore all and sundry have been attempting it. There may indeed be difficulties attending the operation and there may be serious complications, and the realization of these points should emphasize the desirability of entrusting the selection and operation of these children to properly trained laryngological teams.

Basic assumptions.—It is suggested that four basic assumptions be accepted :

(1) Where removal of tonsils and adenoids is indicated this should be complete. The technique employed is immaterial provided that results conform with this dictum.

(2) It is extremely doubtful that there is an internal secretion for these particular pieces of lymphoid tissue, any more than for Peyer's patches to be found in the intestine.

(3) It is a reasonable hypothesis that the tonsils and adenoids are part of a defensive mechanism against infection, specially highly developed at the entrance to the food and air passages and specially active when most needed. For example the enlargement of this tissue in response to local sepsis at various ages is well known; the literature is voluminous.

(4) The defence mechanism may itself become heavily infected and therefore cease to function.

Repeated upper respiratory infections are probably a function of overcrowding in home and school life. The fact that so many children are sent up about their tonsils and adenoids is surely the biggest single argument that we must expect to continue to do a large number of these operations. The tonsil problem, then, resolves itself into a double challenge—to the experts of preventive medicine, and to hospital authorities to provide an adequate number of beds.

Diagnosis.—The problem presenting itself to the laryngologist is whether the tonsils of any given child are harmful rather than valuable. Inspection alone is almost valueless because tonsils will show changes in size and appearance according to the season of the year, and according to how recently the child may have had an upper respiratory infection. The history is of paramount importance, and should be obtained from the parent and the family doctor. The school doctor is less likely to give reliable evidence because he sees the child only at routine inspection, and may not have had a chance to obtain the history from the parents, and almost certainly does not treat the child when ill. Furthermore it is important in evaluating the history to distinguish clearly between the symptoms which might be ascribable to the tonsils and those which might be ascribable to the adenoid tissue. The fact that tonsils and adenoids are frequently removed at the same sitting has led to a good deal of loose thinking and writing, and surveys of results of operation have often been clouded by the fact that the benefits or the reverse have not been ascribed to one piece of tissue rather than the other.

Assessment of adenoidal hypertrophy and infection.

Enquiries here should be directed towards the history of nasal trouble, obstruction, mouth-breathing and snoring. As a result of these questions one may discover that the child is suffering to some degree from sinus infection, and one must not be too sanguine in expecting miraculous cures of this condition by removal of the lymphoid tissue alone. Inspection should include examination of the anterior nares, and for this an aural speculum is found to be extremely useful in small children. Posterior rhinoscopy by means of a mirror is sometimes unsatisfactory, and it is suggested that more use should be made of the naso-pharyngoscope. Digital examination of the post-nasal space in children should be reserved for those cases where there has been a previous adenoidectomy and where there is doubt about residual tissue. Even then that examination is best conducted under general anæsthesia. A high-arched palate, a deviated nasal septum and dental overcrowding form a triad of signs which one should regard as important.

Assessment of the tonsils.

It has been laid down by eminent laryngologists many times that the most certain proof of chronic infection is the occurrence of repeated acute attacks. A peritonsillar abscess (even one) is an indication that the tonsil function has broken down. As has been said the appearance of the tonsils constitutes no clear evidence about whether they should be removed. On the other hand chronic enlargement of glands at the angle of the jaw would suggest that the first line of defence has in fact broken down. Unfortunately the matter cannot be settled by biopsy because morbid histologists are unable to assess the grade to which a tonsil is infected.

Five absolute indications for removal are suggested:

(1) Repeated attacks of acute infection, i.e. more than two.

(2) The occurrence of a single quinsy, though this is uncommon in children.

(3) Cervical glands persistently enlarged in the absence of chronic nasal sinus disease.

(4) Gross hypertrophy causing such obstruction to the air and food passages as to produce symptoms.

(5) Tuberculous adenitis.

In amplification of this last, it would seem a reasonable assumption that in the majority of cases of tuberculous glands in the neck the infective organism enters via the tonsil tissue. In a very large number of cases, tuberculous giant-cell systems can be found in the tonsils of such children. Irwin Moore [4], Scarff and Whitby [5] and Pagel [8] have all written about this topic. Where operation on the glands is proposed it is suggested that this should be carried out before the tonsillectomy, because minor post-operative sepsis of the tonsil-bed may lead to a secondary infection of the gland with breaking down and consequent abscess formation.

In addition, there may be relative indications for the removal of tonsils and adenoids, each of which taken singly would have no real significance. Here again the history is of some

importance. Minor sore throats, attacks of unexplained pyrexia, poor appetite, a dry "tickly" cough having no origin in the chest or nasal sinuses, repeated earache and in general such conditions as are supposedly caused by a focus of infection should all be considered on their merits. The laryngologist, however, would be wise to place major diagnostic reliance upon an actual history of repeated sore throats.

Statistical evidence.—Many statistical surveys have been made in an attempt to assess the value of this operation in children. That made by Kaiser [6] and that by Paton [7] may be mentioned. These surveys are open to criticism from one standpoint or another. For instance it would seem to be important to compare the history of children who have their tonsils and adenoids removed before and after the operation, rather than compare those children with another series who were supposedly healthy. Advice from a statistical expert on this matter suggested that children presenting themselves in the clinic should be divided into two main groups, those who needed the operation and those who did not. Half of the number in each group should have their tonsils and adenoids removed and the other half should be spared the operation. The subsequent history of each sub-group should then be compared with its own prior history, and with the subsequent history of each other sub-group.

It is evident that it would be difficult to reconcile such a survey with clinical honesty.

A brief survey of 337 children upon whom the dual operation was performed in the Radcliffe Infirmary in the last two years has been made by Miss Esmé Hadfield, and her results, though probably not satisfactory to the statistician, at least embody the principle that the children are compared with themselves. It is suggested that no other comparisons are so valid when dealing with methods of treatment of disease in the human subject.

Poliomyelitis and tonsillectomy.—It is generally agreed that the virus of poliomyelitis can be transmitted either by droplet spray or by the intestinal route, and that the latter is the more important. It is suggested that the virus settles in the tonsillar fossæ in recently operated patients and travels straight up the nerve sheath so exposed to the brain. Evidence has been collected that where cases of poliomyelitis closely follow upon tonsillectomy, the type of case is likely to be bulbar rather than spinal. The small number of very dramatic family groups where something of this kind has occurred lend colour to the idea. But it must be remembered that there is no proof that these children had acquired the infection *de novo*, that they were about to develop the disease anyway, or that they were in fact carriers.

Very little can be said with certainty about the epidemiology of this disease, and though it is supposed that the invasion and carrier rates in the child population are very high in the season of peak incidence, it may also be concluded that the immunity rate is high, too.

Scott Stevenson [3] has made a survey of the figures reaching this country from the United States of America and these have been extremely contradictory. In general it seems that the incidence-rate of poliomyelitis in recently tonsillectomized children is about the same as it is in the total child population, but that where such cases do occur they tend to be bulbar and therefore severe. It is necessary to preserve a sense of proportion in this matter, and to remember that the risk of a given child contracting poliomyelitis within a given period of time is less than the risk it runs in crossing a city street. It is suggested that from a public health point of view it is important to weigh that chance against the total good done to the child population by well-chosen operations in the optimum season.

Extra beds.—The waiting list for cases of tonsils and adenoids is something quite distinct from the general list of ear, nose and throat cases. This is, it is suggested, the true "Tonsil Problem". The introduction of the Health Service will, it is hoped, be followed by a very proper diminution of the number of unskilled operations and of the use to which Cottage hospitals are put for this purpose.

Conclusions

(1) Removal of the tonsils has been known as a beneficial operation for 2,000 years at least.

(2) The hypertrophy of the lymphoid tissue calling for operation is due to repeated infections; these being determined by the overcrowded conditions of civilized life.

(3) The number of children continuing to be sent up by their family doctors is in itself the best argument that in selected cases the operation is a beneficial procedure.

(4) The diagnostic criteria now adopted by responsible laryngologists are conservative and sound. Adenoids need separate consideration from tonsils.

(5) The selection of the cases and the operation should be in the hands of specialist teams.

(6) There is a nation-wide shortage of beds, but hospitals could devote beds to no better purpose.

(7) There is no satisfactorily established evidence that the removal of tonsils and adenoids increases the likelihood of a patient acquiring an infection with the virus of poliomyelitis in the epidemic season.

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Miss Esmé H. Hadfield: This pilot survey was made at very short notice and I doubt if the figures are statistically significant although I believe them to be mathematically correct. Altogether 337 children were reviewed. Of these 170 had had their tonsils and adenoids removed in 1947 and 167 in 1948. The cases were in no way selected, and although I have not worked out the age and sex distribution accurately I believe that they are roughly equal in each group. The family doctors of these children were circularized and asked for their comments on their health since operation. Some of their answers were very full and helpful, but the proportion who had lost touch with the children was too high to make it worth while to analyse their statements.

One was very impressed in making the survey by the mothers' answers to the question "is this child better or not for the operation?" Such remarks as "100% better", "a different child", and "she lived on M & B before" occurred with gratifying frequency. However, one was prevented from becoming too smug by the rare mother who produced a long tale of illness which began the moment that the child returned home from the hospital and was still going on.

While reviewing these children I picked up 4 who needed investigation of their sinuses, 3 with allergic rhinitis, 4 with tonsil relics who were still getting severe sore throats, 1 with chronic otitis media, and 10 with unrelated pathological conditions.

My first table shows the percentage answers to the question: "Is the child better or not for the operation?"

	Better	Not better	Don't know	Unchanged
1947	89·4	1·2	4·7	4·7
1948	88·6	1·2	6·6	3·6

Incidence of sore throats before and after the operation.

	Sore throat before none since	Never had a sore throat	Still has sore throat
1947	58·0	30·0	12·0
1948	68·0	23·5	8·5

Incidence of colds.

	More colds	Less colds	Unchanged	Don't know
1947	3·5	74·0	22·0	0·5
1948	0·6	90·0	9·4	0

Improvement or not in hearing. (Of course in the large proportion of children the hearing had never been affected.)

	Better	Worse	Not better	Never affected
1947	15·6	4·3	3·0	77·1
1948	17·0	0·6	4·2	78·2

Snoring.

	Before operation but not since	Never snored	Still snoring
1947	73·0	16·8	10·2
1948	75·0	21·5	3·5

Incidence of aural discharge without symptoms of acute otitis media.

	Before but not since	Since but not before	Before and since	Never
1947	10·6	3·0	5·9	80·5
1948	13·2	0·6	3·0	83·2

Incidence of acute otitis media.

	Before not since	Since but not before	Before and since	Never
1947	8·3	5·3	2·3	84·1
1948	7·6	0·6	1·8	90·0

Present general condition and development of the children.

	Average	Above average	Below average
1947	55·0	28·2	16·8
1948	62·7	26·5	10·8

Only one child had had a subsequent operation on the ears, nose or throat and this child had had a re-adenoidectomy.

Mr. R. Scott Stevenson said that he must take exception to Professor Illingworth's use of the word "irrefutable" regarding the alleged evil influence of tonsillectomy on the incidence of poliomyelitis. The evidence from America, on which this opinion was founded (for there was not enough evidence in this country), was certainly not "irrefutable". For his own part he thought it wrong to found an opinion one way or another on the American evidence, for one publication was cancelled out by another ; if Professor Illingworth quoted Utah in 1943 he could quote against him Wichita, Kansas, in 1940, and so on and on ; there were scores of articles to quote from on each side.

Probably the most reliable authority in this field was D. S. Cunning of New York, who, in recent years, had been collecting statistics from different districts and analysing them in the form of a useful annual report. Cunning (*Laryngoscope*, 1949, **59**, 441), who had studied 17,000 cases of poliomyelitis and 35,000 cases of tonsillectomy, said that he was "quite convinced that no definite causal relationship between tonsillectomy and poliomyelitis had been established". In the Manhattan Eye, Ear and Throat Hospital, among 35,039 children in nine recent years who had had their tonsils operated on, only 5 had contracted bulbar poliomyelitis.

Turning to the subject of tonsillectomy, the attack upon that operation in recent years was in the main by public health officials and had been grossly exaggerated. The Medical Research Council in a report on epidemics in schools in 1938 stated that "there was a tendency for the operation to be performed as a routine prophylactic ritual for no particular reason and with no particular result". Such a remark was merely an impertinence and unworthy of an M.R.C. publication. Dr. Alison Glover's repeated attacks on tonsillectomy were more worthy of attention, but his opinions had been founded entirely on statistic and they all knew what they could do with statistics.

Professor Illingworth was good enough to say that the ear, nose and throat specialist was a better judge than the pædiatrician on whether tonsillectomy should be done or not. He himself felt that the problem was best approached from the point of view of the patient's history, and the child's mother might often make the best judge. Was the child getting sore throats, frequent colds, otitis media ? If the tonsils were giving trouble they should be taken out ; but if they were not giving trouble they should be left alone.

The following speakers also took part in the subsequent discussion : **The President (Mr. R. D. Owen), Mr. H. V. Forster, Mr. Mackenzie Ross, Dr. R. F. Hendtlass, Dr. J. C. McFarland, Mr. W. L. Thomas, Mr. T. A. Clarke, Mr. Munroe Black, Mr. Denis Browne.**

Professor Illingworth, in reply, said how much he had enjoyed Mr. Scott Stevenson's contribution. Mr. Scott Stevenson had stated that Cunning was the most reliable worker in the United States. That was a statement which he could not accept. Mr. Scott Stevenson had further said that he did not believe at all in statistics, and then he had gone on to try to convert them with statistics from Cunning. He himself knew the work of Cunning and had read his articles, but he felt that there were snags in that statistical study. One was that in the questionnaire which was sent out at the instigation of the American Oto-Rhino-Laryngological Society, the results were obtained after the operation had been very largely stopped in the areas where poliomyelitis was most heavily epidemic ; therefore the results were rather obscure. In the areas where there was poliomyelitis a lot of people decided not to do the operation. The American Foundation for Infantile Paralysis recommended that the operation should not be done during the prevalence of a poliomyelitis outbreak.

Section of Neurology

President—JULIAN TAYLOR, C.B.E., M.S., F.R.C.S., F.R.A.C.S.

[*December* 1, 1949]

DISCUSSION ON CURRENT TRENDS IN THE MANAGEMENT OF THE GLIOMATA

Mr. Joe Pennybacker (The Nuffield Department of Surgery, Radcliffe Infirmary, Oxford): As so much of neurosurgical interest in the past ten years has been centred on head injuries, infections, and psychosurgery, I thought it would be salutary to consider a group of cases which comprises nearly half of all intracranial tumours, a group which remains, after more than a quarter of a century of rapid advances in technique, a most troublesome problem for the neurologist, physician and surgeon alike. My survey has been somewhat depressing, how depressing will be apparent as my report unfolds. Our material consists of 716 cases of verified gliomata of the brain dealt with in the Nuffield Department of Surgery in Oxford during the past eleven years.

TABLE I.—INTRACRANIAL GLIOMATA

Cerebellar astrocytoma ..	44	8·52%	
Ependymoma..	17		16·5%
(Cerebellar 10)			
(Cerebral 7)			
Medulloblastoma	57		
Spongioblastoma multiforme	282		39%
Astrocytoma (cerebral) ..	181		
Oligodendroglioma	44		44%
Unclassified	91		
Total	716		

In Table I it will be seen that only just under 9% of these tumours are reasonably benign—these are the cerebellar astrocytomas and ependymomas. If a *cerebellar astrocytoma*, the common tumour of childhood, be completely removed it does not recur and many of our early cases are still alive and well. Much longer survival periods are common but in the present series there are two cases of recurrences eleven and twelve years after a primary removal. This raises the question as to how often complete removal is possible: certainly it is not possible if the tumour extends into the brain-stem, and this occurred in no less than 11 of our 44 cases, i.e. in 25%. But there is every reason for pursuing a cerebellar astrocytoma with the utmost vigour. If an irremovable extension is found, there may still be a long period of useful survival and in one case there has been good evidence of response to radiation therapy.

I have been a little disappointed to find that it is not uncommon for children who have had complete removals done in early childhood to grow up with slight mental defects or behaviour disorders which may lead to difficulties in social adjustment. This may be the result of the long-standing hydrocephalus which usually exists in these cases before they come for treatment. The defect is rarely serious but it may mar what is otherwise a complete recovery.

Two technical matters are worth mentioning. The first is that in the case of infants and small children it is safer to remove the tumour in two stages rather than at one session. At the first operation a decompression is done, the tumour is verified, and if there is a cyst present it is tapped. We then prefer to wait for three to four months to allow an adjustment to the altered pressure relationships afforded by the decompression. At the second operation, the tumour can be taken out with a good deal more safety and less post-operative worry than if the whole procedure had been done in one stage.

The second point is that all of these lesions causing hydrocephalus should be verified if at all possible. There is a current vogue for easy short-circuiting procedures such as ventriculocisternostomy and ventriculostomy for hydrocephalus, and remediable lesions may be missed if care is not taken to be certain just what is causing the hydrocephalus.

Fig. 1 shows the ventriculogram in a boy of 16 who had had periodic occipital headache for seven years, and some unsteadiness of gait for one year. On examination in October 1940 there was some enlargement of the skull, bilateral papilloedema, no nystagmus, and slight generalized unsteadiness of his limbs. The ventriculogram (A–B, Fig. 1) we interpreted as indicating hydrocephalus due to stenosis of the aqueduct, as only the upper part of the aqueduct could be filled and it ended in a sharp point as is commonly seen in this condition. We made an anterior ventriculostomy (incision of the lamina terminalis) and this seemed to be effective as the headache ceased and the papilloedema subsided. But there was little improvement in the neurological status and because of this he was readmitted ten months later and the ventriculogram was repeated. The ventricles (C–D, Fig. 1) were smaller and an air shadow could be seen at the site of the fistula indicating that it was effective. The posterior end of the third ventricle was deformed and we then thought that the lesion had all along been a brain-stem tumour which was now growing up into the third ventricle. He died suddenly two months later and at autopsy there was a large cystic and solid astrocytoma of the vermis. Had we even inspected the posterior fossa in this case, the result might have been different.

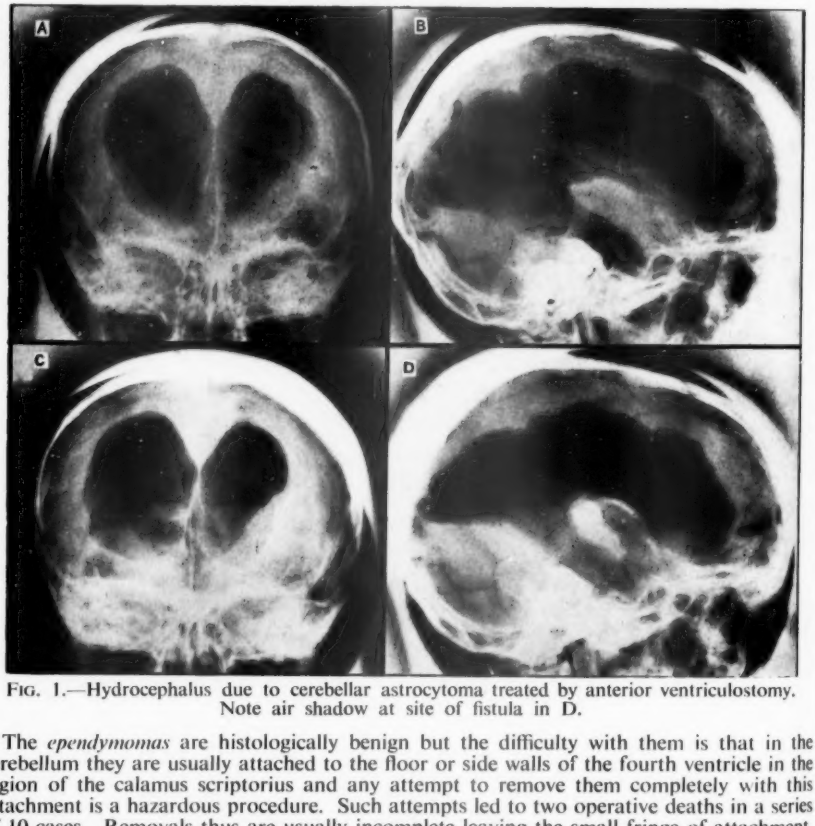


FIG. 1.—Hydrocephalus due to cerebellar astrocytoma treated by anterior ventriculostomy. Note air shadow at site of fistula in D.

The *ependymomas* are histologically benign but the difficulty with them is that in the cerebellum they are usually attached to the floor or side walls of the fourth ventricle in the region of the calamus scriptorius and any attempt to remove them completely with this attachment is a hazardous procedure. Such attempts led to two operative deaths in a series of 10 cases. Removals thus are usually incomplete leaving the small fringe of attachment, but I think we have good evidence that these tumours are radio-sensitive, and that it should be possible to deal with this remnant by radiation therapy after as complete a removal as is deemed safe.

Thus in November 1939 we admitted a child of 7 who, for five weeks, had had severe headache and vomiting culminating in stupor. On examination, she was drowsy, incontinent and wasted. There was bilateral papilloedema of 3D., a little nystagmus on looking to each side, hypotonia and unsteadiness of all her limbs. In addition she complained of acute pain in the right hip and held it in an attitude of flexion and adduction, resisting any attempt at passive movement. X-rays of the skull, spine and hips were normal. We thought that this was probably a medulloblastoma with spinal metastases, and in the rush of work at that time did not verify the lesion or provide a decompression but sent the patient off for a course of radiation treatment. There was a prompt and dramatic response and when she was seen in March 1940 she looked and felt well and there were no detectable abnormalities on examination. She remained well for one year, but in March 1941 there was a recurrence of headache and papilloedema, and she had another course of treatment. Again there was a good response, and she remained free from symptoms and signs for two and a half years.

Again there was a recurrence, but a third course of treatment brought about no improvement and she died in December 1943, four years after the onset of symptoms. At necropsy, the tumour was found to be an ependymoma of the fourth ventricle.

The improvement in this case must be attributed to the radiation therapy as there was no decompression and the skull did not expand by separation of the sutures, a mechanism which often provides temporary relief of pressure symptoms in childhood.

Of the cases verified at operation, one removed in 1939 followed by X-ray therapy has remained well up to the present time. Another removed in 1938 had a recurrence ten years later which was verified at a second operation and then had X-ray treatment with a satisfactory remission of symptoms. Another removed in May 1945 had a recurrence of symptoms nine months later, but a course of X-ray therapy brought about a prompt improvement and she has remained well since then.

In the cerebral hemispheres, the ependymomas have no constant situation and they behave much as any other intrinsic neoplasm. There is thus not the same risk at radical removal as in the cerebellum, but as they are often very large and complete removal cannot be assured we have usually followed operation with X-ray therapy. One case with complete removal in 1941 followed by radiation has shown no evidence of recurrence up to the present time. Another case treated by a bony decompression and X-rays in 1940 remained free from symptoms for five and a half years.

Thus we feel that the proper management of these tumours entails as complete removal as is considered safe followed by a course of radiation therapy.

The *medulloblastomata* comprised about half of the cerebellar tumours, the vast majority of them occurring in childhood or adolescence. And in this series the picture was one of almost unmitigated gloom. When Cushing and Bailey gave these tumours a separate identity the average survival period was about seven months after operation. With the recognition of their radio-sensitivity, and improvements in radiation technique, the average survival period began to lengthen to eighteen months or two years and practically all of our cases succumbed within this time. All which survived operation had radiation treatment, and it has apparently made little difference to the ultimate survival whether an extensive removal has been done or not. I should say, however, that in considering the immediate operative mortality, it seems to be more dangerous to remove too little than too much and we now think that a very radical removal should be attempted if at all possible. This can be more easily done by excising the vermis and the adjacent parts of both cerebellar lobes rather than relying on the mid-line vermis incision which Cushing introduced. But in my view the solution of this problem does not lie with the surgeon. Lampe and MacIntyre (1949) in a recent survey state that surgery has never cured a medulloblastoma: they were unable to find a verified case which survived more than three years when sole reliance had been placed on surgical removal, i.e. without radiation. Spitz, Shenkin and Grant (1947) in an analysis of 97 cases found that of 60 patients under the age of 16 years, none survived longer than three and a half years with surgery and radiation. But these authors call attention to the fact that when a medulloblastoma occurs in adult life the outlook may be a good deal better: among 21 patients with adequate follow-up data, 13 survived three or more years after operation, 9 for four years or more, 4 for five years or more; 3 patients were still alive three, six and eight years after operation. In about half of these cases the tumour was in the lateral lobe of the cerebellum rather than in the vermis. Penfield and Feindel (1947) reported one case of a woman of 22 with a medulloblastoma of the lateral lobe of the cerebellum which was removed in December 1928, and a course of deep X-ray therapy was given after operation. The patient remained well for nine years, when a recurrence of headache and papillœdema led to another cerebellar exploration at which no tumour was found and it was presumed that there was another tumour in some other part of the brain. A second course of radiation brought about a complete recovery for another seven years, when a recurrence of symptoms led to a third course of radiation. The response was less satisfactory this time and she died in October 1945, seventeen years after coming under treatment.

We have had only one example of this relatively favourable group, a man of 35 who had a medulloblastoma of the left lobe of the cerebellum removed in August 1942. A course of X-ray treatment was given after operation and he has remained well up to the present time, seven years after operation. It is thus worth approaching these tumours with somewhat more optimism than is so far justified when they occur in childhood. For the latter, which constitutes the bulk of the problem, surgery must be followed by radiotherapy, and improved techniques do hold out some promise: Lampe and MacIntyre report that although 17 of their 25 patients succumbed within 38 months, 1 lived for 68 months, and 7 (28%) survived for periods ranging from 33 to 92 months (33, 47, 50, 70, 72, 83, and 92). These are the best results that I know of with this type of tumour, and I hope they will stimulate our colleagues in radiotherapy to increase their efforts.

Turning now to the tumours of the cerebral hemispheres which account for about 80% of all gliomata, and about half of which are *spongioblastoma multiforme*.

TABLE II.—SPONGIOBLASTOMA MULTIFORME—282 CASES

Died in hospital		110
Discharged from hospital, deteriorating		83
Major interventions—number of cases		89
Operative deaths	14 (16%)	
Survivors	75	
28 "Deteriorating" in 6 months, no P.M.		
38 died within 16 months		
6 died within 18–33 months		
1 died at 48 months		
1 died at 51 months		
1 alive and well after 51 months		
Useful survivals (longest 51 months)	30	

It has been known from the early days of brain surgery that these are unfavourable tumours, but I doubt whether any of us realize quite how bad they are until we are faced with figures. We operate on these patients, they often get out of hospital, we see them at the follow-up clinic once or twice, and we forget them in the welter of new cases and of the more benign types which keep on coming up year after year. But in fact 110 of these 282 patients died in hospital. In the majority of these, death was accelerated by a ventriculogram and biopsy and in most it was a merciful release. 83 patients survived the procedures involved in verifying the lesion—and in this connexion I should say that arteriography and burr-hole biopsy seem to be a good deal less lethal than ventriculography and biopsy—but in all cases the patient was described as deteriorating on discharge from hospital and there were no useful survivals.

This leaves 89 cases in which the circumstances were such that we considered some major intervention worth while, in most cases with a view to radiation treatment subsequently. These procedures ranged from decompressions to complete removal although usually the removal was known to be incomplete and the operation really amounted to an internal decompression. There were 14 operative deaths in this group, a mortality rate of 16%. Of the 75 survivors, 38 were known to be dead within 16 months, 6 survived for periods from 18 to 33 months, one for 48 months and one for 51 months. One patient is still alive and well 51 months after removal of the tumour (*vide infra*). In all cases recurrence of the tumour seemed to be the cause of death. Of the remaining 28 cases, we have no final note of death, but in almost all of them there was evidence of deterioration within six months of operation, and it is safe to assume that they died shortly afterwards.

These figures relate to the survival period, but if we consider them from the point of *useful* survival, the aspect is even more sombre. Of course the term useful survival is somewhat arbitrary: what might be so regarded by an optimistic surgeon might be quite differently assessed by the patient's relatives, and vice versa. We have taken as a rough standard, a man's ability to return to his work, or to some wage-earning occupation, and in the case of women, the ability to return to housework, shopping, and the care of their family, &c. There is an additional factor and that is the *duration* of useful survival, and this is even more arbitrary than our definition of useful survival. It usually takes at least a month for a patient to convalesce from his surgical experiences, and even though he returns to work for a month, and then has a recurrence, it may be doubted whether this month should count as useful survival, and in my opinion it should not. I see no humanity in snatching a person from the jaws of death, his working for a month or two, and then having to undergo a fatal illness for the second time. Such cases I have discarded, and I find that of our whole material there were only 30 cases of useful survival, 18 of them survived usefully for periods up to 6 months, 3 for 9 months, 3 for 12 months, 2 for 24 months, one each for 30 and 33 months, one for 48 months, and one for 51 months.

The general trend of these figures has been apparent for several years, and to be realistic about these tumours in the present state of our hospital services, the most important thing about them is histological verification. All of us have had the experience, not once or twice but many times, of being faced with the case in which there is every reason to diagnose a rapidly growing glioma, and which at operation or autopsy proves to be a meningioma, subdural hæmatoma, abscess or the like. The differentiation cannot be made on clinical evidence, nor will electro-encephalography, ventriculography or arteriography always provide the right answer. We have seen a practitioner with an almost unique experience of arteriography mistake a spongioblastoma multiforme for a meningioma, and on the next day making the opposite mistake. The only certain way is histological verification and this means a biopsy after accurate localization by arteriography or ventriculography. In cases in which there is already profound disability such as aphasia, hemiplegia or mental derangement, and when the diagnosis of spongioblastoma multiforme is proved histologically, we think surgery has nothing to offer. Heroic operations may prolong existence for a few months, but this usually means that some other member of the family is sacrificed to look after the invalid, and the social havoc which may result from such surgery is often appalling.

The situation may be a little different in those cases in which increased intracranial pressure is the dominant factor and there is little neurological or mental deficit. Such lesions are apt to be in the frontal, parieto-occipital or minor temporal lobes, and there may be something to be said for extensive removals. In this series, the extent of the removal has not appeared to make a great deal of difference to the ultimate survival. Professor Russell and I have previously reported a case (1948), not included in this series, of a right frontal spongioblastoma multiforme, treated by decompression and several courses of radiation treatment, which survived for seven and a quarter years. In this case the amount of tumour removed was only sufficient for histological study. On the other hand, in a clinically comparable case in this series a tumour weighing 114 grammes was removed from the right frontal lobe in October 1948 with a gratifying immediate result, but headache recurred within three months, fits in six months, with death at ten months. At autopsy the large operative cavity in the fore-part of the right hemisphere had been completely replaced by tumour (Fig. 2).



FIG. 2.—Brain from which 114-gramme spongioblastoma multiforme had been removed ten months before death. Note massive recurrence.

Early diagnosis.—On general grounds it might be supposed that if we could get these tumours early enough, and remove them when they are small the outlook might be better. In this connexion I should mention 2 cases:

The first was a man of 37, who was operated on in August 1939. He had a small, apparently circumscribed glioma in the right mid-frontal cortex measuring 2·5 cm. in diameter. It was removed completely with a liberal surrounding of normal white matter, and we thought that the outlook was good, as this seemed to be a small tumour, detected early, and removed completely. This patient was dead in January 1940, five months after operation, and at the autopsy the tumour measured $9 \times 9 \times 6$ cm. and occupied both frontal lobes and the corpus callosum. He had had no X-ray treatment.

The second case is a woman of 38, who had a tumour of about the same size (3 cm. in diameter) removed from the cortex of the right parietal region in August 1945. It, too, appeared to be circumscribed, and was removed in a block of tissue measuring $6 \times 4 \times 3$ cm. She had a course of radiation after the operation and is alive and well at present, 4¼ years after operation.

These two cases stress at once the despair and the unpredictability which attend the surgery of the gliomata. They also add emphasis to a theme which has kept recurring throughout my remarks, that surgery alone is powerless in the management of many of these tumours and that the combined efforts of surgeon and radiotherapist are essential. In conclusion I would like to mention a case which we have in hospital at present:

A woman of 34, who was admitted in November 1939, with headache, vomiting, occasional epileptic attacks, papillœdema, some mental derangement and little in the way of other physical abnormalities. The ventriculogram (Fig. 3) we interpreted as bespeaking a bifrontal glioma invading the corpus callosum and septum lucidum, and inoperable. She was provided with a subtemporal decompression and had a course of X-ray treatment and remained quite well for nine years, until October 1948 when she reported with a recurrence of symptoms. The decompression was tight, she had papillœdema, stupor, &c., and a further course of treatment again brought about a dramatic response. She was again seen in October 1949, free from symptoms but in early December there was a recurrence of headache and vomiting leading to her readmission. The ventriculogram was repeated and it was essentially similar to the one ten years before. At operation, an astrocytoma weighing 128 grammes was removed from the right frontal lobe, but the tumour could be seen to be invading the corpus callosum as well.



FIG. 3.—Ventriculogram in bifrontal astrocytoma.

This result I think can only be attributed to the radiation and we have a few cases of almost all types of glioma which have seemed to respond at least for a time and to some extent. Most of us realize the limitations of surgery, and although radiotherapy alone is not sufficient, I regard the recognition of its proper role in conjunction with surgery as the most significant trend in the management of the gliomata.

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Mr. D. W. C. Northfield: For my contribution to the Discussion I have chosen only a few of the commonly accepted groups of gliomata, and they come from the period of approximately 1939–1944. They include several cases from the time when Sir Hugh Cairns was at the London Hospital, patients who have since then been under my observation. I shall not deal with the cerebellar astrocytomas, the medulloblastomas, or the gliomata of the brain-stem. There are 58 cases of glioblastoma (spongioblastoma) multiforme in which a full follow-up is available. Many of these patients died in hospital without major craniotomy, although in such some diagnostic measure was usually employed in order to confirm the diagnosis. In the others an attempt was made to remove the tumour as completely as seemed compatible with useful existence, and radiotherapy was given in many. The results are such as Mr. Pennybacker has described; an occasional patient survived for over a year, in fact 4 for over two years. But one patient is still alive and deserves comment.

At operation in 1943, six years ago, the tumour—a small one in the frontal lobe—was removed with a good margin of brain. The patient received X-ray treatment and returned to work. Four years later in 1947 there were focal signs suggestive of a recurrence, but these mostly disappeared spontaneously and were presumably the result of a focus of radionecrosis. There has been no further evidence of deterioration.

The next group comprises 39 cases of cerebral astrocytoma, and in Fig. 1 is set out a graphic representation of the length of history in years before operation, and of post-operative survival. The queries denote some doubt as to the precise length of history, and the precise date of death. In 7 patients death occurred without any operation, or following biopsy by needling, and in another 7 death followed major craniotomy. In some no attempt was made to remove the tumour, in others the removal was frankly partial and therefore recognized as palliative, in a few it appeared to the naked eye that the tumour had been removed completely. The late results appear unaffected by the operative procedure. There have been a few cases of long survival; up to a maximum of seven years in a woman now dead in whom the tumour quite obviously was inoperable, but the seven years were useful years during which she became happily married. 3 patients have lived for over five years, and 6 for over four years. 2 patients are still alive, one $5\frac{3}{4}$ years after evacuating a cyst, and removing some tumour for histology; and in the other the tumour appeared macroscopically localized and was thought to be completely extirpated. This impression was given support by Dr. Greenfield's statement that microscopically the tumour had

a sharp edge. Both patients are living useful lives. Many of these tumours have a very long natural history—a point to be remembered.

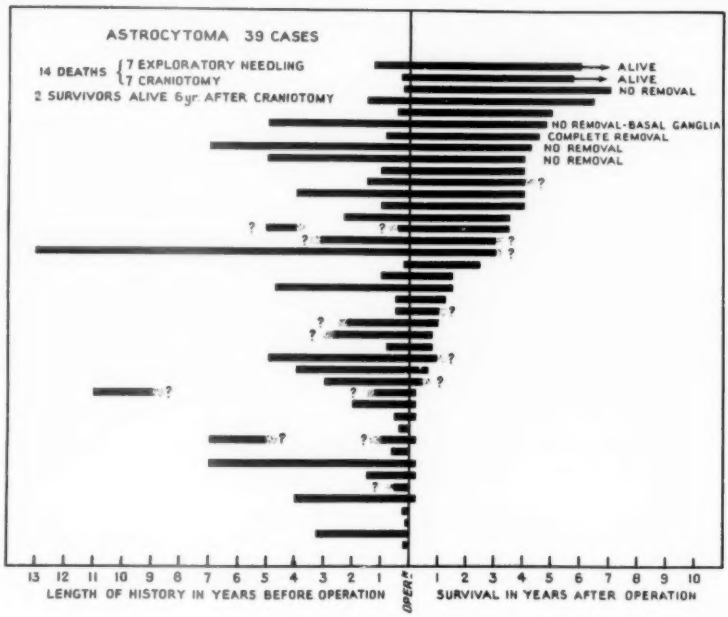


FIG. 1.

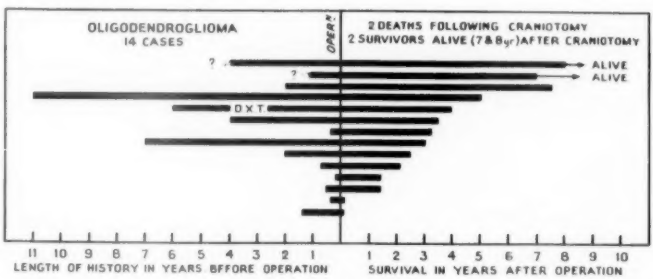


FIG. 2.

Fig. 2 deals with cases of oligodendroglioma of which there are 15 examples (14 only on the chart). All patients were subjected to craniotomy, from which 3 died, and the surviving 12 subsequently received X-ray treatment. One is still alive after what appeared to be total removal eight years ago, but he is handicapped by epilepsy; this tumour was histologically designated as rapidly growing and mitoses were seen. Another patient lives seven years after a known incomplete removal of a shaggy vascular intraventricular growth, and she is very well and has worked hard throughout this time. The patient dying 7½ years after a radical operation in 1935 by Sir Hugh Cairns, had signs of a massive recurrence and received X-ray treatment in 1938 and again in 1940 with obvious benefit on each occasion. This chart brings out a point which I think is of fundamental importance in the understanding of gliomata—their biological behaviour. The cases with long pre-operative history are usually those with long post-operative survival. The initial symptom in these long stories, as in the astrocytoma group, is usually epilepsy, and operation is an interlude demanded by the symptoms of raised intracranial pressure, or by the evolution of a neurological defect. In this connexion the following case is instructive, and is the one not charted.

A man was admitted in 1936 to the London Hospital under Sir Hugh Cairns on account of left-sided focal epilepsy of approximately a year's duration; there was a history of several head injuries, and a scar was present at the vertex in an appropriate position for the focal epilepsy to be considered

possibly post-traumatic. There was only equivocal weakness of the left limbs. X-ray of the skull showed a fleck of calcification in the right frontal lobe, and an encephalogram showed some dilatation of the right ventricle. Exploratory craniotomy revealed shrunken gyri, no biopsy was performed, and the diagnosis of post-traumatic epilepsy seemed correct. He was observed regularly, and his fits fluctuated in degree and in frequency. In 1948, that is thirteen years after the onset of fits, they became worse, and the slight weakness of the left limbs became more definite. Encephalography now revealed a typical tumour defect, and at craniotomy a massive oligodendroglioma was encountered; he died shortly afterwards.

The other group of hemisphere gliomata I wish to mention are the ependymomata. There have been only 5 in the period under review, 3 in the third ventricle, 1 in the lateral ventricle and hemisphere, and 1 in the cerebrum not apparently attached to the ventricle. The results have been bad. 2 of the third ventricle tumours died as a result of the operation; the third died of a recurrence a year after operation, at which the tumour seemed to be completely removed, as it appeared only lightly adherent to the walls of the ventricle. Of the lateral tumours, one survived a year; the other three-and-a-half years, a second attempt to remove a recurrence of the tumour which seemed completely removed at the first being equally fruitless. My experience with the fourth ventricle tumours is similar to that of Mr. Pennybacker; provided the enucleation is complete—and this endeavour may make the operation lethal—the results are as good as with the cerebellar astrocytoma.

The treatment of gliomata is a gloomy business, with the exception of certain well-defined entities, viz. the cerebellar astrocytoma and ependymoma. But there are the occasional cases which survive for long periods, whatever procedure is carried out, and these at first sight seem to confuse rather than to clarify the picture. This I believe is due to a fundamental misconception of the nature of the tumours we are dealing with. The surgeon is apt to believe when he removes apparently completely a compact mass of tumour—perhaps a so-called mural nodule in the wall of a cyst—and histologically diagnosed as an astrocytoma that he has removed a benign tumour. But surely nothing is further from the truth. Carmichael in 1928 and Scherer more recently have shown very clearly that the astrocytoma is a diffuse and infiltrating tumour, extending microscopically far beyond the confines of the macroscopically visible tumour. The use of the adjective "benign" for a glioma is a misnomer if it implies, as it should, an encapsulated tumour. Scherer divides the manner of growth of the gliomata into expansive and infiltrative; expansive growth pushes aside brain tissue with a minimum of infiltration, thus simulating a benign biological characteristic. He states that only the ependymoma has this manner of growth, and that not always. Growth by infiltration is shown by all other gliomata to varying degrees, and moreover this property does not correspond with the malignancy of the cells. The cerebral astrocytoma he considers the most invasive of all gliomata, but amongst the glioblastomata some 20% are found in which invasiveness is relatively circumscribed. The oligodendroglioma is similarly less invasive than the astrocytoma. The other important distinction which Scherer emphasizes, which we probably all appreciate but do not constantly bear in mind, is that invasion by tumour does not necessarily mean the destruction of the nervous tissue involved; invasion can occur with, and without, destruction. This is of great clinical importance in the natural history or the biology of the slow-growing astrocytoma and oligodendroglioma. Tumour may be present for many years, perhaps causing epilepsy but causing no significant neurological deficit. Such patients may ultimately need operation for the relief of raised intracranial pressure, the evacuation of cysts, and partial removal of the tumour may provide a useful internal decompression, but the surgeon cannot hope to do more.

Another problem is the varying histological picture which a tumour may present in different areas. If the surgeon receives a report that the tissue he removed is a glioblastoma, he has no assurance that the part left behind may not be predominantly astrocytoma and more slowly growing, and so his case of glioblastoma will perhaps survive for a surprisingly long time. The reverse holds true, that his patient with an astrocytoma may die in a few months, and if he has not the fortune to obtain the brain he will not learn the histology of the remaining part of the tumour which may be anaplastic.

If we examine again the chart of astrocytomata we find that some show long histories, with long post-operative survival. Others of this group show no such relation, and in others the evolution has been entirely rapid. Surely the explanation of these anomalies is that the group is not a homogeneous one, but a mixture of cases of slowly growing and of rapidly growing tumours and probably varying their invasive and destructive powers. They have different biological qualities which are not reflected in the name astrocytoma, which is attached to them.

Finally, in the surgery of the glioblastomata we have to face the possibility that in some patients, even if the tumour be removed with a good margin of healthy tissue, there may be a recurrence, not as a result of leaving behind some of the tumour, but because of the multicentric origin of some glioblastomata.

The present practice in the treatment of gliomata is, in the first place, an attempt at a pathological diagnosis. This may often be suspected from the clinical picture, and

angiography may give valuable help. Clearly when there is doubt between a glioblastoma and a meningioma, the old-fashioned method of placing greater reliance on clinical judgment than on ancillary methods will usually lead to exploration. In some cases, the circumstances will suggest biopsy by needling; in the series of glioblastomata under review this was undertaken in 40 patients, providing a positive histological diagnosis in 13, equivocal findings such as cyst fluid or a doubtful histological report in 14, and it was uninformative in 13. If a glioblastoma is diagnosed, the trend nowadays is to avoid operation, and this I believe to be correct when the tumour is invading eloquent areas of the brain. But in certain cases operation should be carried out, on humane grounds to relieve suffering where death is not imminent, and in those cases in which there is some reason to believe that a total enucleation may be possible. In these cases, more surgery and more *radicai* surgery seems the right direction in the future.

It has been shown that a glioblastoma may possess a false line of cleavage around its margin. This may be due to a narrow marginal zone of necrosis, misleading to the surgeon, who by following this plane leaves behind a thin rind of active tumour. In other cases the tumour is surrounded by gliosis, a form of capsule, which makes for easy removal of the apparently localized tumour. But on histological examination, tumour cells will be found permeating the white matter beyond the zone of gliosis. Thus in these tumours the surgeon removes a very wide margin of healthy brain if he hopes to extirpate the tumour. Unfortunately many of these tumours are already at the time of operation too extensive to allow of this.

The surgeon sorely needs some ancillary aid which will inform him whether or not he has got well beyond the tumour. The use of such things as fluorescein would seem to be an important help, indeed any method of showing up tumour tissue would be an outstanding advance in the surgery of gliomata.

The cerebral astrocytomata should at present be regarded as being irremovable in most patients. Operation is often necessary to relieve symptoms of raised intracranial pressure, and this incident having been successfully passed, surgery probably has little more to offer. The oligodendroglioma in some cases can only be dealt with on similar lines, but there is no doubt that when a tumour seems to the surgeon to be localized, he should endeavour to extirpate it. My experience with the cerebral ependymomas has been small, and—in spite of Scherer's statements—the results disappointing. Nevertheless extirpation should be the method of choice until we know more about them. Before leaving the surgical aspects of gliomata, I would like to raise the question of non-dominant hemispherectomy for a tumour such as an oligodendroglioma or perhaps an astrocytoma which by such a radical procedure might be completely and permanently removed. I was much impressed by the recent report by Bell and Karnosh of such a case of astrocytoma, the patient being alive and well ten years afterwards. It would appear that the consequent disability is not so severe as might be expected. I think the possibilities of such operations should be explored, at any rate tentatively, and would be justified in view of the present position of the treatment of gliomata.

Finally a word must be said about radiotherapy for gliomata. An increasing number of such tumours are being treated in this way, and, in truth, we have nothing else to offer after the surgeon has performed some palliative operation. It is difficult to obtain a parallel series of cases with and without radiation, for no two cases are alike, and the similarity or otherwise of the tumours cannot be determined until a post mortem has been made. The comparison cannot be made as with, say, a series of cases of pituitary adenoma. But we have all seen individual patients in whom, judging by clinical methods, there is no shadow of doubt that radiation has caused retrogression of the tumour to a greater or less degree. And this holds good for each of the common types of glioma. Yet the hope of ultimate cure is negligible. This is a problem to be solved by the radiotherapists, and I cannot help feeling that eventually the treatment of extensive malignant growths in general will lie in this direction, or with some similar physical method as yet undiscovered, or else along a biological approach. In the meantime it appears that radiotherapy leaves much to be desired. With the advent of high voltage apparatus, radionecrosis has become a recognized danger. There is also the possibility that at the borderline of maximum tolerance of the brain tissue, certain changes around a glioma described clearly by Carmichael and which may be a defence mechanism against invasion, may be endangered. Some of the unpredictable and surprisingly long survivals after partial removal of gliomas may be due not to radiation entirely, but to natural defences. If the brain has a natural defence against certain gliomata, it should never be damaged by irradiation. This is a problem to be studied along with that of the optimum time—dose factor for the gliomata.

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Dr. Gerald Parsons-Smith: In a series of 150 verified cases of cerebral tumour I found that the electroencephalogram had some diagnostic value in cases of cerebral glioma. The E.E.G. should show a focal abnormality in the affected hemisphere in the great majority of supratentorial gliomata even before the patient develops abnormal physical signs. Although such a unilateral focus was found in 88·5% of astrocytomata and 87% of the malignant gliomata, the position of the maximum electrical abnormality was found to coincide with the actual site of the glioma in only 74% in each group. The E.E.G. should not be employed to demarcate the *anatomical limits of a glioma*, as this can usually be done more accurately by the various radiological methods, but rather it should be used to illustrate *the extent and the degree of the abnormal brain tissue around a tumour*, and also the direction of the tumour spread. It was a comparatively easy matter to distinguish the infiltrating lesions from such conditions as cerebral abscess and subdural hæmatoma, but the E.E.G. appearances produced by the various gliomata were not specific and it was not possible to differentiate between them. After operation and deep X-ray therapy the earliest evidence of recurrence of a glioma could be found in the E.E.G. which also reflected the slightest change in cerebral metabolism produced by the progress of a tumour in the posterior fossa.

Mr. G. K. Tutton: The experience from Manchester in Professor Geoffrey Jefferson's Clinic is almost exactly comparable to that recounted by Mr. Pennybacker and Mr. Northfield.

I would agree with them that the outlook in all but one or two cases is most depressing. Although there have been at least two cases of survival for twelve and fourteen years which support Mr. Northfield's contention that more radical surgery should be the rule, we now believe that a more realistic view towards the gliomata in the cerebral hemispheres should be adopted.

Operations on the glioblastoma multiforme, except those made for a biopsy, are rejected so far as possible.

We try to make a precise pathological diagnosis by arteriography, and where the typical appearance of these tumours is shown no operation is suggested.

Extensive internal decompressions for palliation and social reasons are sometimes done for these tumours in the frontal lobes.

In my opinion the most significant trend in the management of the gliomata is the present emphasis placed on the *pre-operative assessment* of the pathology of the tumour.

Unquestionably the development of percutaneous angiography, which, unlike ventriculography, does not necessitate immediate subsequent operation, is at present the most valuable means of attaining this end.

I have analysed the last 100 cases of glioma in the cerebral hemispheres seen in the Neurosurgical Service in Manchester during the past eighteen months.

There were 55 glioblastomata, 37 astrocytomata, 5 oligodendrogliomata, 1 ependymoma and 2 unclassified.

Angiography was performed in 31 of the glioblastomata and in 27 of these a typical tumour pattern was seen. In only 4 was there no pattern. In general the massive vascular marking with numerous abnormal vessels gave the diagnosis, and in many cases we were thus able to avoid craniotomy.

A diffuse blush in the arterial phase sometimes led to difficulty but we have learnt that the blush of a meningioma usually occurs in the phlebograms.

Secondary tumours, of which there were 10 in the same period, can mimic the typical appearance of a glioblastoma and in 3 of them there was a diffuse blush in the phlebograms which suggested meningioma. 22 angiograms were done in the 37 astrocytomata and all but 2 showed no tumour pattern at all. However, there was obvious distortion of one or more of the main cerebral vessels. In the two with the tumour pattern the diagnosis of astrocytoma was made on the sections although macroscopically we thought the tumours to be glioblastomata.

I think this apparent anomaly could be explained by dedifferentiation in these tumours.

The numbers of the remaining gliomata are too small for useful analysis.

We have also found the electroencephalogram of great value in localising the side of the tumour for subsequent arteriography. In our experience chronic subdural hæmatoma and cerebral abscess can nearly always be diagnosed by the electroencephalogram.

In view of the great shortage of hospital beds major operation on the gliomata are, therefore, avoided as far as possible.

After clinical examination an electroencephalogram is done to find on which side the tumour is situated if this is not already known.

If a percutaneous angiogram is equivocal as it is with mid-line tumours and some of the astrocytomata, ventriculography or encephalography is done.

The number of ventriculograms has fallen by nearly one-third.

Section of Medicine

President—Sir ADOLPHE ABRAHAMS, O.B.E., M.A., M.D., F.R.C.P.

[*January* 24, 1950]

DISCUSSION ON OBESITY

Dr. A. W. Spence: The pathogenesis of obesity is difficult to understand. It is my usual experience to have obese patients referred to me as suffering from what is termed "some endocrine disorder", or from "pituitary dysfunction", or as cases of hypothyroidism. The matter, however, is not so vague nor so simple as that, for in the bulk of cases there is no obvious evidence of any endocrine disturbance whatsoever. This does not mean that an endocrine disturbance is not the cause, but the suggestion that it *is* the cause is hypothetical. I propose to discuss mainly the pathogenesis and treatment of the condition.

PATHOGENESIS

The endocrine system. The Gonads.—The gonads have priority because from the earliest times castration has been practised in order to fatten livestock. From this experience it would seem that the fattening process in these animals is dependent on a deficiency of testicular secretion. The typical picture conjured up of a eunuch is that of a very obese person, but though it is true that eunuchism and eunuchoidism may result in obesity, this is not always so; eunuchs are said to be approximately one-half tall and slender and one-half short and fat. A cross section analysis of normal men is not greatly different (Moore, 1935).

Only one testicular hormone has so far been isolated, namely testosterone, and in my experience and in the experience of others testosterone has little effect on the obesity in these conditions.

It is well known that obesity may occur in women at the time of the menopause, but neither œstrogen nor progesterone is effective in reducing the excess of fat, and obesity is not a feature of ovarian infantilism in which there is a failure of ovarian development. Experimentally there is no definite evidence that the administration of the male or female sex hormones exerts any influence on fat metabolism, although perhaps testosterone may increase the storage of fat.

Thyroid.—A common fallacy is that obesity is often due to hypothyroidism. Many of the patients thus labelled have none of the features of hypothyroidism and a determination of the basal metabolic rate is inaccurate owing to the large surface area of the body. Although obesity may occur in myxœdema and hypothyroidism, it is not the rule, the thyroid being more concerned with protein than with fat metabolism.

The adrenals.—It is probable that the adrenal cortex produces compounds which affect the metabolism of fat and cause obesity. Gross obesity may occur in patients with an adrenal cortical tumour. It is usually not characteristic of the androgen-producing tumours which give rise to the adrenogenital syndrome, but it is a feature of those adrenal tumours which are responsible for Cushing's syndrome. These tumours produce corticosterone and corticosterone-like hormones. Kendall (1945) has shown that the administration of corticosterone or of 11-dehydrocorticosterone to certain strains of mice increases the amount of fat in the animal. However, the experimental evidence of the existence of an adrenal hormone which promotes the deposition of fat is meagre. Albright (1943) has suggested that the obesity associated with adrenal tumours is due to excessive conversion of protein into glucose by corticosterone and the subsequent conversion of glucose into fat.

Pancreas.—Obesity may be caused by hyperinsulinism, due to a tumour or to hyperplasia of the islets of Langerhans. Although a low glucose tolerance curve is present in a high proportion of adipose persons, and Lawrence (1941) has shown that an important action of insulin is the conversion of carbohydrates into fat, there is no clear evidence that their obesity is due to excessive secretion of insulin.

Middle-aged diabetics are often fat. I tentatively suggest that sometimes obesity combined with hyperglycæmia may possibly be the result of adrenal hyperfunction and may be in the nature of an incomplete Cushing's syndrome.

The pituitary.—The pituitary gland is usually implicated as being the cause of obesity, a popular diagnosis being "pituitary dysfunction", which could mean either hyperpituitarism or hypopituitarism. The common belief that hypopituitarism is a frequent cause of obesity dates from Fröhlich's original description of obesity occurring in children with a pituitary tumour and from the early experiments on partial ablation of the pituitary, whereby the animals so treated became obese. I cannot subscribe to this view. Although it is true that obesity may be associated with a pituitary tumour, it is equally true that it may not be.

The thyrotrophic hormone is the only pituitary hormone a deficiency of which may possibly cause obesity. The combination of pituitary infantilism and obesity, however, is rare. The low basal metabolic rate observed in Simmonds's disease and other forms of hypopituitarism is presumably due to deficiency of thyrotrophic hormone and yet these patients are not obese—in fact, the opposite is often the case.

With regard to hyperpituitarism, obesity may occur in acromegaly and in Cushing's syndrome. For this reason it has been suggested that the adiposity is due to hyperpituitarism. Against this opinion is the observation that acromegalics as a whole do not tend to be fat. In my view the obesity of Cushing's syndrome is due to hyperfunction of the adrenal cortex, secondary to hyperpituitarism. Some observers have affirmed, however, that the obesity of Cushing's syndrome is only apparent, the bulging abdomen being due to osteoporosis (Albright, Parson and Bloomberg, 1941).

Simpson (1948) has ascribed puberty obesity and climacteric obesity to hyperactivity of the anterior pituitary. This is possible, but it is more likely to be through its action on the adrenal cortex rather than through a primary effect.

Pregnancy.—It is not uncommon for obesity to occur rapidly after pregnancy. The cause of this is obscure, but during pregnancy there is undoubtedly hyperfunction of the anterior pituitary and of the adrenal cortex.

Over-eating.—Obesity has been classified as endogenous, when it arises through some disturbance within the body, and exogenous, meaning that over-eating is the cause—a classification which is falling into disrepute. The suggestion has been made that some of these patients have a pathological hunger akin to the pathological thirst of diabetes insipidus and it has been postulated that this is due to excessive secretion of insulin, as I have already indicated. I do not consider, however, that over-eating is responsible for many cases of obesity; in my experience the majority of patients affirm that they eat little. If over-eating is a factor, the problem of obesity is somewhat simplified, but not entirely solved, since some thin people have hearty appetites and yet remain thin.

The hypothalamus.—The hypothalamus may play a greater part in the genesis of obesity than is generally supposed. Smith (1926) showed that obesity was produced in his laboratory animals not by removal of the anterior pituitary, but by injury to the tuber cinereum. It is

probable that in the earlier experiments in which obesity occurred after removal of the pituitary the hypothalamus or tuber cinereum was also damaged. Hetherington and Ranson (1942) showed that the presence of the pituitary is not essential to the appearance of hypothalamic obesity. Clinically, it is well known that obesity may arise as a sequel to diseases such as encephalitis and meningitis which damage the hypothalamus.

Those pituitary tumours which cause obesity probably do so, not by interfering with pituitary function, but by pressing on the hypothalamus. The obesity of Fröhlich's syndrome is due not to a pituitary but to a hypothalamic lesion. It has been shown that there are centres in the hypothalamus which regulate menstruation via the anterior pituitary and that disturbance of these centres by impulses from the higher centres, produced by emotional causes, results in amenorrhœa (Theobald, 1936). This condition is not infrequently accompanied by obesity, suggesting that other centres in the hypothalamus are also affected. Although it has been established that there are nervous and vascular connexions between the hypothalamus and the pituitary, I doubt whether hypothalamic obesity arises as a result of a secondary disturbance of anterior lobe function, as in the case of amenorrhœa, (1) because of the animal experiments already mentioned, and (2) because clinically there may be no evidence of anterior pituitary disturbance.

On the other hand, it may be argued that it is rash to consider a disordered hypothalamus as a cause of obesity when other evidence of hypothalamic disturbance is absent. I do feel, however, that the hypothalamus may be the centre of a weight-regulating mechanism, whatever that mechanism may be, which controls the breakdown and storage of fat. A different "gearing" of this mechanism may explain certain cases of sporadic, familial and racial obesity.

Water retention.—Water retention may be present in obese patients and this may even be shown by pitting œdema. Associated with the retention of water there may be diminished excretion of sodium chloride. Harris (1947, 1948) has demonstrated that stimulation of the neural stalk of the pituitary in rabbits produces inhibition of water diuresis. Verney (1946), who found that water diuresis in the dog can be inhibited by subjecting the animal to muscular exercise or emotional stress, has suggested that this is due to secretion of an antidiuretic hormone by the posterior pituitary. There is also evidence that the anterior lobe promotes diuresis (Shapiro, 1938), an intact anterior lobe being necessary for the polyuria of diabetes insipidus. Hence the water retention which may accompany obesity may be due to disordered function of the hypothalamus, resulting either in increased secretion of the posterior lobe antidiuretic hormone or in decreased secretion of the anterior lobe diuretic hormone.

From this review it will have been seen that we know very little concerning the causation of obesity.

Obesity in children.—In my experience any child who is fat is labelled as having Fröhlich's syndrome, especially if there is present what appears to be genital hypoplasia. Fröhlich's syndrome is rare and is caused by an organic lesion affecting the hypothalamic-pituitary connexions. The commoner syndrome resembles Fröhlich's syndrome in its clinical features, but it differs from Fröhlich's syndrome in that it is not caused by a gross pathological lesion; sexual development is merely delayed, and after puberty a good deal of the fat is lost spontaneously.

Treatment

Endocrine obesity.—Endocrine obesity is obesity due to an obvious endocrine disorder. Loss of weight may follow removal of or radiotherapy to a pituitary tumour and the obesity of Cushing's syndrome may respond to removal of the adrenal tumour—if this be the cause—or to irradiation of the pituitary. In hypogonadism, although testosterone does not cause loss of weight, some of the flabby fat may be lost as a result of its use. If hypothyroidism is the cause the administration of thyroid results in loss of weight, but otherwise its use is disappointing. The increase of weight at the menopause is unaffected by the administration of œstrogen. In all cases of obesity the administration of pituitary extracts is valueless.

Reducing diet.—The fundamental treatment of most cases of obesity, i.e. those which have no obvious endocrine disturbance, is a reducing diet. Such diets consist of a very low fat and carbohydrate content and, because of its specific dynamic action, a high protein

content, the total calorie value per day being about 1,000 calories. The diet, being deficient in vitamins A and D, should be supplemented with a vitamin concentrate. As there may be a retention of sodium chloride and water, fluids should be limited to 2 pints a day and the intake of salt reduced to a minimum.

It is a remarkable fact that sometimes weight is lost more rapidly when the patient is treated at rest in bed than when up and about.

Patients should lose about 2 lb. a week. When the desired weight has been reached, the diet should be increased, but not so much as to cause a further gain in weight. Most patients will always have to be careful of their food intake.

Dextro-amphetamine.—5 mg. of dextro-amphetamine may be given before breakfast, at 11.0 a.m. and at 4.0 p.m. to reduce appetite, should patients find adhering to the diet difficult. At the same time it induces a sense of well-being and as far as I am aware in these doses it has no harmful side-effects.

Thyroid is rarely necessary, but it may be given in conjunction with the diet if results with the diet are unsatisfactory. In my experience obese patients are often resistant to the action of thyroid. In these cases there is no point in giving more than 3 grains a day.

Diuretics.—In view of the water retention which may be present, diuretics are theoretically indicated, but I cannot say that I have been much impressed with their effects in obesity. A mercurial diuretic is given intramuscularly in doses of 2 c.c. two or three times a week.

Physiotherapy.—Exercise will help a little, but not so much as is generally thought. For most obese patients it is exhausting. Massage, purgation and Turkish baths are of very limited value.

In children.—Whether a reducing diet should be given depends on the degree of obesity. In general it should be avoided, for it is a hardship; further it is doubtful whether the child will keep to it and in boarding schools it is impossible. Thyroid is unnecessary if there is no evidence of hypothyroidism. Usually little improvement is obtained unless it is given in toxic doses which is undesirable. It is well known that many children who are overweight lose their excessive weight spontaneously after puberty.

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Professor E. C. Dodds: Excluding the classical syndrome with an endocrine background associated with obesity, there is very little to say about its cause or treatment that has not already been said many times over. The treatment consists either of disguised starvation; or of some form of increasing the energy output such as the stimulation of the metabolism by hormones, for example, thyroid, specific dynamic action by proteins, polynitrophenols such as dinitro-ortho-cresol, and exercise.

All of these methods have been reviewed at very great length and we know that thyroid extract is no answer to the problem because one has to produce far too great a rise in metabolism to effect sufficient consumption of fat to cause loss of weight. Specific dynamic action is unfortunately out of the question owing to the difficulty of getting meat, whilst the polynitrophenols are too dangerous because of the fear of death from hyperthermia and of a development of cataract.

Again exercise is a very severe method of counteracting obesity as one has to perform such a lot of exercise in order to reduce weight. Some years ago I made some calculations which I published in an Address at the Middlesex Hospital, and these melancholy findings have been quoted as a warning to fat people on several occasions. For example, it can be calculated that the maximum output of energy for short periods is at the rate of 600 calories per hour. Very few people can maintain this rate and the average person will find great difficulty in putting out more than 300 calories in a half-hour game of squash rackets. This is equivalent to two slices of bread and butter, or alternatively, two dry Martinis. Every pint of beer requires half an hour of squash, or, if the person is not capable of expending energy at this rate, the equivalent of a five-mile walk would just about equal it. A glass of champagne corresponds to about ten minutes' squash whilst a double whisky and soda would require the full half-hour.

An even more depressing calculation is that during an average dinner in pre-war days something between 700–800 calories could be consumed in the form of alcohol. In order to work this off it would be necessary to play squash for five and a half hours, or alternatively, to climb Ben Nevis several times.

The real problem with which we are concerned is that we do not really understand the mechanism of weight regulation. General experience shows very clearly that subjects fall under two headings: (*a*) people who maintain a constant weight over many years despite excessive intake of food, and (*b*) the second group who respond immediately to an increase in calorie intake by the putting on of weight. Between these two groups there are subjects who vary in their power to put on weight according to intake. The two main groups have been noted by many clinicians and many explanations have been put forward to account for the persons who remain at a constant weight despite their calorie intake. The two most important suggestions are, firstly that their digestion or absorption is poor with the result that a considerable proportion of the food passes out undigested and unabsorbed in the fæces. The second theory to account for the maintenance of weight at a constant level is that the metabolism of these subjects is stimulated by the food they eat and that they have an exaggerated specific dynamic action.

Dr. Mary Ransome and I have performed a number of experiments of which the following is a brief summary:

The first investigation consisted of taking people who had a record of constant weight over many years and assessing their normal dietary intake. The subjects were then given an intake of double and treble their normal, and in some cases they were kept in bed. We had little difficulty in confirming that there did exist this group who, under the most carefully controlled conditions, failed to put on weight even when given excessive quantities of food. A careful analysis of the fæces failed to indicate any increase in the output of nitrogen or fat. Microscopic examination showed very clearly that the digestion was normal. This confirmed what has already been published by a number of other workers, namely that the explanation on the lines of comparison of digestion and absorption cannot be advanced in this case. Whilst it is too early to give a very definite statement, our respiratory metabolism investigations indicated quite clearly that these subjects responded to a high diet by an increase in their basal metabolic rate, whereas the corresponding controls who put on weight readily, showed no such increase. This line is being actively pursued, and may provide additional evidence for the view that the explanation for the phenomena of the person with the constant weight is that they have a much more resilient metabolism capable of being stimulated to deal with a sudden increase of food.

I prefaced my remarks by stating that we knew very little about the mechanism of weight control and I think very few people realize that an astonishing mechanism must be in constant operation. If one weighs the subject at the same time of the day, say on rising in the morning, the weight of the individual is astonishingly constant, assuming that the subject is neither gaining nor losing weight, the weight remains constant to within roughly 1 lb. and this means, in the person of average weight, a reproducibility of between 0·5% and 1% on a weight of over one hundredweight. This is astonishing when one considers to what influences the body might be subjected in twenty-four hours, such as varying degrees of exposure, output of fluid, perspiration and so forth.

One only has to think of the elaborate mechanism which is required to maintain definite weights in a submarine or an airship to realize that there must be some underlying mechanism of very great delicacy in all animals.

This mechanism must obviously be related to something external. For example, we know that the onset of the mating and nesting of birds in the spring is associated with the intensity of light falling on their heads and necks, we know that the maintenance of temperature is due to the sensitivity of the skin through its nervous supply responding to the external temperature, thus causing sweating, &c., and I feel that there must, therefore, be some external factor to which the body reacts to keep weight constant. If one thinks about the situation it must almost certainly be that the body reacts to gravity and it is possible that there is some relation between the body and the gravitational pull. I have thought a good deal as to how one could investigate this and have conducted a series of preliminary experiments which, on occasion, have caused my colleagues to doubt my mental stability.

The ideal experiments would be to lessen the gravitational pull and, if the theory is correct, the body should increase in weight. Experiments with coal-gas-filled balloons strapped to arms of subjects could not be maintained for a sufficiently long period to evoke any response other than mirth and sardonic comments. A further attempt was made with rats supplied with chain mail binders and exposed to magnetic pull from above. This again proved to be quite impracticable. Again the weighting of subjects with sandbags introduced so many complications about the increase in work to uphold the sandbags that the experimental results defied analysis.

It appears that there is only one way to investigate this problem and that is to have an experimental centrifuge containing animals such as rats and mice and to accustom them to living their lives to revolutions. It would then be possible to adjust the speed of the centrifuge to control the gravitational pull. The design of such an instrument would, of course, be very complicated and up to the present no one has done anything in this field.

Dr. Raymond Greene [*Abstract*]: Much of the speculation and experiment about the origin of "obesity" is misdirected owing to its emphasis on fat instead of water. If we believe that people are overweight because of an excessive deposit of fat, we are confronted by a series of insoluble dilemmas in the face of which we must either deny the law of the conservation of mass, or change our beliefs. I prefer the latter alternative. Fat can only come from food, even the most vegetative patients being unable to manufacture it from the atmosphere. If an excess of that food is to be laid down as fat we are forced to postulate that the intake is excessive, the absorption abnormally efficient or the use abnormally deficient. Each proposition has been disproved by many reliable investigations. Fat people do not eat more than their fellows, and their absorption, their metabolism and their specific dynamic action are normal. We are forced by cold logic to believe that the excessive weight of these patients is not fat at all. If then we ask what it is, the answer is ready to hand. Clinical and experimental evidence shows that "adiposity" may be caused by damage to the hypothalamus, in which lies the nucleus supra-opticus, the central control station of water metabolism. Damage to this region by concussion or encephalitis or its derangement by such severe emotions as anxiety and depression often cause a rapid increase in weight. I pointed out in 1946 the similarity between the increase in weight so common in anxious women and the now classical experiments of Verney on dogs subjected to equivalent emotions. More direct evidence comes from the fact that pitting œdema is almost always demonstrable in the very "fat", usually along the shins; from the excellent results of a dehydrating regime even when this supplies ample calories; and by a single (and therefore unreliable) experiment of my own which I have never found time to extend: I assayed the true fat content of two cylinders of equal cross section of adipose tissue from the abdomens of two women, one "fat" and one thin. Though the one cylinder was four times as high as the other, the fat content was almost equal.

I conclude that the "fat" person is one whose adipose tissue is overhydrated rather than overfatted. The distribution of his "fat" depends upon the distribution of his adipose tissue. People do not keep their "sponges" in the same place, though most people seem to have one in the abdominal wall. "Fat" people differ from those whose water retention is due to cardiac or renal causes in that their excess of fluid is concentrated in their adipose tissue. Why this should be we cannot yet say, though we may guess that fluid storage is one of the physiological functions of adipose tissue.

Finally, I would like to support Dr. Spence in his condemnation of thyroid and anterior pituitary extracts in the treatment of obesity. The former in small doses may be useful as a diuretic, but urea is a better one. Apart from this slight activity it is useless in safe doses except in those rare instances in which hypothyroidism is present. The use of the latter is absurd. In the unlikely event of the anterior pituitary being to blame at all in "obesity", the fault is in the direction of overactivity. Moreover pituitary tablets are completely destroyed by the normal processes of digestion.

The President said he was one of those who have been described as possessing a weight-regulating mechanism, whatever that meant. For the past forty years he had, with the most minor fluctuations, remained at a constant weight without any restrictions in the nature and quantity of food. It had been suggested that an explanation was afforded by his addiction to regular fairly strenuous exercise but as Professor Dodds pointed out no such relationship appears to be pertinent. On the basis of oxygen consumption, the calorie value of all forms of exercise is readily computed, a litre of oxygen being the equivalent of 5 calories. And taking 1 lb. of fat as a standard of calculation, the exercise necessary for its combustion is that comprised in walking nearly 70 miles at the reasonable sustained speed of 3½ miles an hour. Needless to say the increased ingestion of food consequent on the appetite produced would more than counterbalance the loss of fat. If really violent exercise were in question, one would have to run at the rate of 10 miles an hour for 43·2 miles, to row from Putney to Mortlake nine times; or, were such a feat humanly possible, to run at full speed for 7¼ miles—say 21½ minutes for the same loss of fat.

Incidentally, one possible fallacy might be mentioned, loss of weight must be distinguished from loss of fat. He had lost 3 lb. in weight in half an hour's vigorous climbing in Switzerland and he had observed a loss of 9 lb. in a runner over a Marathon race of 26¼ miles in about two and a half hours. This was, of course, mainly water which was restored during the ensuing forty-eight hours.

He was, however, tempted to believe that there was some relation between regular exercise and metabolism although investigations *ad hoc* did not appear to support the idea of a constant higher level.

Dr. John S. Richardson: The psychological aspects of obesity are well recognized and quite extensive literature has accumulated on this subject. I shall therefore confine myself to describing a small group of cases that have recently been under investigation by Dr. H. J. Shorvon and myself at St. Thomas's Hospital. In two or three cases of marked obesity which failed to respond to dietary restriction, we found that their history contained a notable traumatic incident. The bombing of a home, the loss of a child, the desertion or suicide of a husband are examples, and were followed immediately by a rapid increase in weight. It was thought that this sudden trauma might well have led to impulses from the cortex acting on the hypothalamus in a manner calculated to alter water excretion and appetite or weight control. I wish to stress that these cases did not show any psychological disorder obvious to me, nevertheless Dr. Shorvon agreed to give them abreactions so as to see if anything would come out of it. Something did, as the abreactions produced a response that was startling in the intensity of the emotion that was released. We have now got some 20 of these cases under observation and I wish to record very briefly the results of the investigation of 12 and the treatment of 9 of these.

They were all married women between the ages of 21 and 42, the majority being round about 30. They showed considerable obesity of simple distribution in all cases save one, that was typical of the so-called "pituitary" obesity. Their family history was interesting in that it showed that in one-quarter the parents were unsatisfactory or frankly bad, in another quarter one or other parent was unsatisfactory, while in half both parents were either good or mediocre, but the father was almost always strict and the mother over-indulgent. The patients' previous personality study and medical history showed that only one, who was a psychopath, had had periods of instability, and their intelligence was average or above average in all cases except this one. Three-quarters were childless and two-thirds had had no knowledge of sexual matters before marriage and most had not made satisfactory sexual adjustment. None of them had been fat before the traumatic incident which was single in 9 and multiple in 3 cases. All showed a rapid and considerable increase in weight after it, associated with irregular periods in 5 cases and amenorrhœa in 2.

Dr. Shorvon found hysterical symptoms in 3 cases, obsessional tendencies in 3 and anxiety traits in 2, and the psychopath to whom I have already referred. They are therefore a group of formerly slim, young married women of average intelligence without previous neurotic illness who were mostly unhappy at home and rigidly brought up in sexual ignorance.

All 9 cases who had abreactions lost weight that, expressed as a percentage of their weight before treatment, averaged out at 13%. The average length of time it took to lose this weight was six months, the average number of abreactions done during this time was twelve. In none of these 9 cases was there a failure to lose over a stone in weight although no other weight-reducing method was employed, but one case that did not have abreactions made no response whatsoever to rigid dieting and dehydration methods. This loss of 13% of the body weight before treatment may be compared with a loss of 23% in married women of the same age treated for the same time as out-patients with dietetic restriction and benzedrine.

I wish to make it quite clear that we do not consider abreactive techniques as a treatment for obesity. What we do say is that these techniques have shown that traumatic incidents followed by obesity in some women are associated with an extremely high emotional content that may well be unsuspected by the general physician or practitioner as the patients do not appear neurotic in the commonly used sense of the word. The release of the emotions by abreactions has been followed in all 9 of our cases by a considerable loss of weight in spite of the fact that no dietary or other measures were adopted. We hope therefore that abreactions may be helpful in managing certain selected cases of obesity by giving relief to a previously unsuspected disorder with subsequent loss of weight.

Dr. W. S. C. Copeman thought that the two points which had been made by the preceding speakers—namely adiposity and abnormality in the distribution of body fluid—could be considered merely as differing aspects of the physiology of fat.

The actual deposition of fat in abnormal quantity was of course of basal importance. He also believed, however, that in man, as in the camel, fat constituted a normal water-storing organ, and that rapid changes both in quantity and in tension could occur under certain circumstances. These changes could give rise to clinical signs and symptoms in the patient.

Section of Comparative Medicine

President—REGINALD LOVELL, D.Sc., Ph.D., M.R.C.V.S.

[*December* 21, 1949]

DISCUSSION: HÆMOLYTIC DISEASE OF THE NEW-BORN

Dr. R. R. A. Coombs (*Department of Pathology, University of Cambridge*): My remarks on the theoretical basis and comparative side of this disease may be considered under four headings:

(1) *Some factors in the pathogenesis of the human disease which are imperfectly understood.*—By 1946 our knowledge of this disease, from the clinical side, could have been viewed with some satisfaction: the diagnosis could be confirmed unequivocally by serological tests and the perfection of the techniques of transfusion and exchange-transfusion appeared to be reducing the mortality rate substantially. Simultaneously workers in blood-grouping laboratories were continuing their most fruitful work in disentangling and characterizing further subgroups of the blood-cell antigens which may be responsible for the disease.

From the biological point of view, however, we were no closer to understanding in what way the natural safeguards against iso-immunization in pregnancy operated. It is difficult to believe that there is any teleological purpose in eliminating at birth certain heterozygous children. If such a purpose exists, it would merit investigation but I think the converse of this line of thought will probably prove more helpful; namely, how does Nature in nearly all cases of pregnancy guard against the consequences of an immunization of the mother by antigenic body constituents of the embryo determined by genes derived from the father? In considering fœtal antigens we must include not only red-cell constituents but all body constituents and extra-embryonic fœtal tissues as well.

If one considers from the theoretical point of view various aspects of hæmolytic disease of the new-born the following appear to be some of the problems still waiting to be satisfactorily answered.

(i) What is Nature's exact protective mechanism against iso-immunization of pregnancy in matings heterospecific as regards especially the A, B and O antigens and also other antigens and in what way does the Rh system of antigens and their related biological phenomena differ from this?

(ii) What is the protective mechanism at work in the many normal pregnancies resulting from a mating of an Rh positive to an Rh negative person where the infant is also Rh positive?

(iii) What are the factors determining the many varied clinical manifestations which may result from iso-immunization with the D antigen?

(iv) What determines the much greater antigenicity of certain of the Rh antigens for the human subject?

Bearing these problems in mind we may now consider what may happen at various stages both during and after pregnancy, by taking the case of any hypothetical blood or tissue group antigen inherited by the fœtus from the father and which is foreign to the mother.

The first matter to consider is how early or late in fœtal development this substance manifests itself in an antigenic form in the embryo tissues themselves or in the fœtal placental tissues which may be more important.

Secondly, how antigenic is this substance? The A and B and certain of the Rh substances are very antigenic but some, such as M and N and other Rh substances, are apparently less so.

Thirdly, do fœtal antigens reach the maternal tissues in every pregnancy and, if so, are they necessarily still in an antigenic form? It may be that during fœtal metabolism these substances in the embryo or fœtal placental tissue become degraded and reach the maternal tissues in a non-antigenic form—but here, depending on the constitution of the mother as one may postulate in certain allergic conditions, the substances may couple with maternal protein and so become converted into potential antigens again.

At this stage one might encounter the first natural safeguard against the possibility of iso-immunization of pregnancy. For instance, the heterologous fœtal antigens may be fixed in the maternal placenta by free or even sessile specific receptors and while anchored they may be degraded locally before being able to reach the antibody-producing tissues of the mother. However one must bear in mind the possibility of the production of antibodies by the local placental tissues of the mother.

The fœtal antigens if not fixed by the maternal placenta may enter the maternal circulation and produce an immunization if the host is susceptible to such an immunization—I stress "if the host is susceptible" for at the moment we divide persons into Rh positive and Rh negative, by whether they contain the Rh antigen on their red cells or not. However, it does seem at least hypothetically possible that some persons so classified as Rh negative although containing no Rh positive substance on their red cells may yet contain this substance as a constituent of some other tissue cells and so would not be susceptible to immunization with the Rh positive substance. I do not think this is the case, however, especially in the light of reports that about 46% of Rh negative persons receiving random or Rh positive blood in the form of transfusions have been shown to produce Rh antibodies (Pickles, 1949). Nevertheless it is a concept which should be kept in mind.

Supposing the process has reached the stage where the mother has produced antibodies against fœtal antigens, there remain further ways in which the fœtus could be protected.

In the first place the placenta in many animal species is fairly impermeable to the passage of antibodies into the fœtus. This may not be such a good protection as it may seem at first and this matter is reconsidered later. Meanwhile we may consider what may happen in the case where the placenta is permeable to the passage of antibodies. In the fœtal placenta there is again the possibility of the maternal antibody being neutralized by free or attached specific fœtal antigen and thus protecting the fœtus itself from the action of the antibody. This is considered to be very likely in the case of the A, B, and O antigens, and may also take place with certain of the Rh antigens; however, this seems unlikely in the latter case for, were it so, one would expect to find many Rh positive infants showing no evidence of the presence of maternal antibody although their mothers showed a definite post-partum rise in antibody titre. Van Bolhuis (1948) found that 16 out of 121 placentæ from Rh positive infants were capable of neutralizing the D Rh antibody, but rather than allowing this to be a protective mechanism the author lays on this fact the responsibility of the immunization of the mother. He came to this conclusion because when he examined the placentæ of Rh positive affected infants 27 out of 31 showed this inhibitory action on the Rh antibody. A confirmation of this work would be most valuable.

We may now reconsider the animals whose placenta is impermeable to antibodies. In these cases the maternal antibodies become concentrated in the first colostrum, the protein of which may be absorbed in its native state by the new-born animal through the alimentary canal. By this route there would seem to be no further possible specific barrier to neutralize the maternal antibodies before they reach the tissues of the new-born animal. So the two modes of protection might have to be weighed up: (*a*) Passage of antibodies *in utero* with the possibility of a specific neutralization in the fœtal placenta, or (*b*) protection from the antibodies till the neo-natal stage with no opportunity of a specific neutralization.

Finally we must consider what may be the significance of the maternal antibodies gaining access to the fœtus or new-born animal and sensitizing some of its cells, whether blood cells or tissue cells. Is this sensitization *per se* lethal to the actual cells themselves or the animal as a whole? One calls to mind cases of acquired hæmolytic anæmia after splenectomy. Dr. Heard's observations on rabbits are also pertinent to this question.

Such are the problems which arise in considering a hypothetical case of an antigenically incompatible pregnancy but another very important matter which must be mentioned is kernicterus. A vital question here is whether the neural lesions are due directly or are in any way related to the specific action of the Rh or other antibody, or are they non-specific in the immunological sense and due to a high concentration of hæmolytic or other degradation products. The distribution of the lesions could well be due to local concentrations of the Rh substance in these tissues. Dereymaeker (1949) believes that the lesions are due to a specific immunological action and he records experiments showing that the tissues of these nerve centres are capable of absorbing Rh antibodies. The fact that the blood-brain barrier in the adult is practically impermeable to antibodies does not vitiate this hypothesis for the blood-brain barrier of the late fœtal or early neo-natal infant might have quite different physiological properties.

(2) *The experimental production of the syndrome in laboratory animals.*—In 1946 we considered that it would be much easier to investigate these varied problems if we could produce the syndrome of hæmolytic disease experimentally in a laboratory animal; we chose the rabbit because we believed it to have a placental structure fairly similar to that of the human. The results of this investigation are described by Dr. Heard but it may be said, that so far as our experiments have gone, the rabbit may not fulfil the requirements we desire for this work.

We then attempted to produce the syndrome experimentally in the guinea-pig and the results of this investigation are described by Dr. Mynors. Work on these two animals, however, is still in progress and further experiments may throw some light on the biology or pathology of this disease.

(3) *Studies on the comparative side of the disease in certain domestic animals.*—In 1948 the opportunity arose to study the disease in thoroughbred horses and in mules, a study which was interesting from both the standpoints of comparative pathology and veterinary medicine.

Caroli and Bessis (1947) were the first to draw attention to the condition of icterus gravis in new-born mules and to show that it was due to an iso-immunization of pregnancy. Previously this condition, which is said to cause an 8% mortality of new-born mules born in the Poitou district of France, had been attributed to piroplasmosis. In the 1948 foaling season Caroli and Bessis invited me to France and together we investigated the serological procedures for diagnosis by techniques analogous to those used in the diagnosis of the human disease. Bessis was also experimenting with exchange-transfusion as a therapeutic measure in mules.

In the same year at Cambridge and Newmarket a large team of workers investigated the condition in new-born thoroughbred foals (Coombs, Crowhurst, Day, Heard, Hinde, Hoogstraten and Parry, 1948). Out of 9 cases of neonatal jaundice we confirmed by serological tests that six were due to iso-immunization of pregnancy. These cases were investigated from their clinical, serological, pathological and hæmatological aspects.

In America, Bruner, Hull, Edwards and Doll in numerous papers have described their experiences since 1947 with this condition in foals and have made many interesting observations. (Bruner, Hull and Doll, 1948; Bruner, Hull, Edwards and Doll, 1948). These workers have also described experiments on this syndrome in new-born piglets (Bruner, Brown, Hull and Kinkaid, 1949)—a study which I feel will repay further investigation and may throw light on piglet anæmia.

Experimental work on producing this syndrome in dogs has been carried out both by Eyquem (1948) who was studying particularly the cerebral lesions and their relation to kernicterus, and by Young, Erwin, Christian and Davis (1949). The latter also refer to a report by Abelson on what appeared to be naturally occurring cases of hæmolytic disease in new-born dachshunds.

The study of this disease in animals is all the more difficult on account of the fact that we know so very little about their blood groups. We are now producing at Cambridge anti-globulin sera for the diagnosis of the condition should it arise in bovines, pigs, dogs and cats;

and we already possess diagnostic sera for humans, horses, rabbits and guinea-pigs. We would be very pleased to examine the blood of suspected cases in any of these species. A small sample of clotted blood from the new-born animal is all that is required for the laboratory tests.

(4) *Some experimental laboratory investigations on problems having a direct bearing on the disease.*—Returning to the human disease, it can be appreciated how important it is to know the exact distribution of the Rh substance in the body; whether it is found in secretions or tissues other than the red cells. Boorman and Dodd (1943) found that the Rh antibody was absorbed by most of the organ tissues of Rh positive persons. The organ suspensions were prepared by grinding post-mortem material and washing it free of the blood constituents. They found no absorption by similar material derived from two Rh negative persons. It would appear from these results that the material from the two Rh negative persons did not contain the antigen in the tissues. In the case of the experiments with tissues from Rh positive persons, although Boorman and Dodd's conclusions that these tissues contain the antigen seem highly probable, there is the possibility of small amounts of red cell stromata still being present in these tissue suspensions and being responsible for this absorption. However these authors had considered this and were confident that the absorptions were due solely to the presence of the Rh substance in or on the actual tissue cells.

Dereymaeker, as already mentioned, demonstrated absorption of the Rh antibody by certain tissues of the brain. Van Bolhuis also showed the presence of the substance in a proportion of placental tissues and Witebsky and Mohn (1945) demonstrated an apparently soluble form of the substance in a percentage of amniotic fluids.

It may be that studies on this aspect of the problem will shed light on the syndrome and at Cambridge, in collaboration with Dr. Boursnell, we are starting work on this question by attempting to demonstrate the presence of the Rh substance in the various tissues with the aid of Rh antibodies tagged with a radio-isotope. Ganglion cells in the brain and the placental tissues will be among the first tissues to be studied.

A very important study is that of the isolation, identity, standardization and therapeutic application of the so-called Rh hapten (Carter, 1949).

Dr. Lythgoe of the Department of Organic Chemistry at Cambridge has, on two separate occasions, prepared extracts from about 400 c.c. packed washed Rh positive cells strictly according to Carter's published specifications. In both cases we have not been able to show any specific activity against the D Rh antibody whether using the specific inhibition test or the complement fixation reaction. We have also tested a sample of the hapten sent to us by Dr. Carter which she said was active at a dilution of 1 : 3,000. Again we could not show any inhibition of the D antibody. We find this most puzzling and can offer no explanation at present, unless it is connected with some very delicate physical state of the substance.

There are a host of problems connected with hæmolytic disease in man and animals which are awaiting elucidation. Many of these problems could be studied best by reproducing the disease experimentally in a laboratory animal for in this way the process could be followed by experimentation through the various stages of its development.

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Dr. C. A. Holman: I have been asked to confine my observations to the human aspects of hæmolytic disease. Table I shows an analysis of the last two years' work at Lewisham Hospital during which time my laboratory has recognized 164 cases of Rhesus iso-immunization in women attending the local ante-natal clinics. The results of these pregnancies were as follows:

TABLE I.

20 born dead	Miscarriage	2
	Macerated stillbirth	6
	Hydrops fœtalis	11
	Stillbirth (prolapsed cord)	1
104 born alive—Cell Coombs–Positive (i.e. affected)	Death from icterus gravis	8
	" " kernicterus	6
	" " cerebral hæmorrhage	3
	" " prematurity	1
	Survived—developed kernicterus	4
	" normal to date	82
14 born alive Rhesus positive Cell Coombs–negative	All normal and survived	14
26 Rhesus negative	Survived—normal	24
	Died—of prematurity	2
		164

The Rhesus antigen D has been shown to be the commonest cause of human hæmolytic disease. Other Rhesus antigens C, E, c and C^w have been occasionally involved as has the Kell antigen. In the present series the D antigen or D and C together were responsible in 162 cases and E and c in one case each.

It is not possible to provide an accurate picture of the incidence of the various types of the disease as, although we are now able to diagnose almost all the cases, the measures taken to combat the disease may alter the severity of the cases and will certainly modify the clinical manifestations. The present series was likely to be modified by the practice of inducing labour at 36 weeks, or as soon afterwards as the infant appeared to have achieved a satisfactory weight. In the first half of the period reviewed, almost all of the affected children received replacement transfusion whereas in the second half only those with cord hæmoglobin levels of under 14 grammes % were given this treatment.

Surveying the detail of the chart one sees the low incidence of miscarriage which I think implies that hæmolytic disease is not usually responsible for death of the fœtus in the first three to four months of fœtal life. The relative proportions of macerated stillbirths and hydrops fœtalis were the reverse of those seen prior to induction of labour, suggesting that the earlier delivery prevented maceration occurring in so many cases and that the macerated stillbirth is simply a later stage in the same process. The proportion of stillbirths has been reduced although that of very severe icterus gravis is greater, which means that there is not a great change in the total mortality. If, however, an infant is born alive there is at least a chance of saving it. It appears to me from the pattern of the disease that hydrops fœtalis is the result of the same process which produces icterus gravis and is just a more severe manifestation.

It is now possible to recognize the mildest degrees of the affection by the use of the Coombs' test and it is clear that a weakly positive Coombs' test is compatible with a normal child who shows neither jaundice nor anæmia. I feel that the induction of labour at 36 weeks helps some children to escape altogether, i.e. the group which are Rh positive and Coombs' negative. This is not unreasonable in that it is known that placental permeability increases at this time. Even if, as had been suggested, the Coombs' reagent is not always powerful enough to demonstrate weak sensitization, it is still clear that a proportion of the infants escape the effects of the disease.

With increasing degrees of sensitization the picture becomes clinically indistinguishable from physiological jaundice and all grades were seen from this to severe icterus gravis and hydrops fœtalis.

It is possible to see marked sensitization of the cells leading to severe jaundice and anæmia in a matter of hours or more slowly over one or two weeks. In some cases serious anæmia never develops. Why some infants show rapid hæmolysis and others do not is not clear. The best prognostic feature is the level of the hæmoglobin in the cord blood. As Mollison has shown, where this exceeds 14 grammes%, severe anæmia is unlikely, while if below 14 grammes% transfusion will almost always be required.

The degree of anæmia depends upon the capacity for regeneration and the rate of hæmolysis, both of which factors show considerable variation from case to case. It is still not clear why hæmolysis takes place as it is possible for sensitized cells to remain in circulation for long periods without destruction or to disappear very rapidly. *In vitro*, experiments show that complement may assist hæmolysis but that, even so, the rate is very slow.

A further matter that is little understood is the degree of jaundice resulting. This appears to depend upon the relative rates of hæmolysis and of elimination of bilirubin by the liver. The liver in the young child has a poor excretory capacity particularly in the premature infant. In the more severe cases it shows enlargement and marked extramedullary hæmopoiesis and has often been subjected to a severe degree of anæmia.

In considering the problem of kernicterus, further complexity is introduced since some of the most severe cases of jaundice show no significant degree of anæmia and yet have sufficient cerebral damage to cause death.

The cause of the damage to the brain is not clear but it is generally thought that the bile pigment is not directly responsible but is deposited in damaged tissue. Prompt replacement transfusion does not prevent it and it seems probable that the damage occurs in the antenatal period. I think that it is probably due to a direct action of the antibodies and that this hypothesis seems reasonable since once the red cells are saturated with antibodies, the free antibodies in the blood stream would, by virtue of the arrangement of the fœtal circulation, be chiefly delivered to the brain and the liver, which organs are most commonly affected after the blood.

Of the other variables which make the understanding of the disease difficult, the most interesting is the occasional variation from pregnancy to pregnancy where one sees infants with the same Rh gene subjected to the same or more powerful antibodies, and yet the later pregnancy will sometimes be less severely affected.

In conclusion, one must remember that although much progress has been made in the treatment of the disease in the live-born infant and in the recognition of its various manifestations, there is, as yet, no satisfactory method of helping the infant before birth and that much more has still to be learnt about the mechanism by which the antibodies produce their effects.

Dr. Dorothy H. Heard (*Department of Pathology, Cambridge*): When we were looking for an experimental animal to use for the investigation of hæmolytic disease of the new-born, we heard from Professor Nachtsheim (Professor of Genetics at the Kaiser Wilhelm Institute in Berlin) that he had by chance found a stock of rabbits some of whose young were born dead or moribund showing marked œdema. He considered that the condition was analogous to hydrops fœtalis in infants caused by hæmolytic disease of the new-born (Nachtsheim and Klein, 1947). In collaboration with Dr. Peter Dahr preliminary serological investigations were begun.

However post-war conditions in Berlin made it difficult for Professor Nachtsheim to maintain his stock of experimental animals and he sent some of these rabbits to Cambridge for safe keeping and for further investigation.

The rabbits were mated and the red cells of all baby rabbits were tested for sensitization by maternal antibody using goat anti-rabbit globulin serum. The does' sera were also tested for an antibody to the red cells of the buck to which they had been mated.

No antibodies were detected by these methods after three pregnancies. Accordingly 19 does were injected with whole blood from bucks to which they were later mated. The experiment was repeated using the same rabbits.

The final results were that 9 does formed antibodies in their sera. 6 of these antisera directly agglutinated the appropriate red cells but in 3 cases antibodies were demonstrated only after using an indirect sensitization test. 4 of the does who formed antibodies in their sera had between them 7 litters in which the red cells of young, inheriting a paternal antigen incompatible with their mothers' antiserum, reacted positively to a direct sensitization test. Nevertheless even the offspring whose red cells reacted positively appeared clinically normal. A proportion of the young were killed when three days and twenty-four days old and hæmatological and histological examinations were made (Heard, Hinde and Mynors, 1949).

The conclusion reached was that maternal iso-antibody may be attached *in vivo* to the red cells of baby rabbits which have inherited a paternal antigen against which their mother has produced an antibody and that this happens without affecting the baby rabbit clinically. It is not yet certain whether the antibody passes to the baby by way of the placenta or the colostrum or both. There is no more than an indication that this sensitization is accompanied

by any derangement of the hæmopoietic system or lesion of any other tissue and, from the results of this experiment, the variations between animals showing *in vivo* sensitization of their red cells and normal animals can be explained as lying within the physiological range.

These findings support the possibility that red cells can be sensitized *in vivo* without affecting the physiological function of the red cells or the individual. The reason that these animals did not show any marked pathological changes may very well be related to the active and immature hæmopoietic system the baby rabbit has at birth.

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Dr. Lavinia S. Mynors (*Department of Pathology, Cambridge*): The sequel to the rabbit investigations described by Dr. Heard was the attempt to reproduce the syndrome of iso-immunization of pregnancy in the guinea-pig. This animal seemed likely to have two advantages over the rabbit in its longer gestation period and the greater maturity of its erythropoietic system at birth. The experiments have been on the same lines as those just reported. 12 guinea-pig does were mated, and injected during pregnancy with the blood of the buck to which they were mated. Their offspring were examined for anæmia, and for evidence of sensitization of their red cells by maternal antibody, and the ante-partum and post-partum sera of the does were examined for antibodies to the bucks' cells. No abnormality or sensitization was discovered in the baby guinea-pigs, and no evidence of an antibody in the sera of the does.

A further attempt to produce iso-antibodies was made with a series of 25 guinea-pig does, each receiving two courses of injections of blood from a panel of 25 guinea-pig donors. Each received contributions from 10 or more donors, and up to 4 injections from the same donor. Again no trace of antibody was discovered in the post-inoculation sera. All these guinea-pigs have now been mated to bucks from whom they have already received blood: their families are not yet born. The experiment is not complete until these offspring have been tested for evidence of sensitization and anæmia, and the ante-partum and post-partum sera of the does examined for antibodies to the bucks' cells, but we can say at this stage that there is no reason to think that we can produce a hæmolytic syndrome in guinea-pigs by this technique. Not only this, but we have produced no antibody at all, in spite of these repeated injections of foreign blood. Although other workers have reported failure to demonstrate normal guinea-pig iso-antibodies, they have not attempted, as far as we have ascertained, to produce immune iso-antibodies by the methods we have been employing.

Dr. J. M. Alston: Dr. Mollison has told us that Dr. Diamond in Boston is less satisfied than formerly with the benefit of inducing labour early as a means of treating hæmolytic disease in erythroblastotic infants. Has Dr. Mollison been able to make up his mind about the benefit of exsanguination transfusion of the newly born infants?

Dr. P. L. Mollison replied that he thought there was no doubt that exchange transfusion was a good method of treatment and that it had certain practical advantages. However, he did not consider that its ability to lower mortality and morbidity had yet been decisively demonstrated. What was needed was a controlled trial in which simple transfusion and exchange transfusion were given equally early to cases chosen at random. Such a trial was now in progress.

Dr. A. E. Mourant: Dr. Coombs referred to the question of the position of hæmolytic disease in the scheme of Nature. I cannot suggest any function which is useful but as the instance of mules shows, where 10% of the young die of the disease, it must have some effect in perpetuating the differences between varieties within a species, once these varieties have been set up by breeding in isolation: it will thus tend to lead to the development of new species. Its effect is certainly less in this respect than that of cytological barriers to interbreeding but it is nevertheless probably significant.

With regard to the possible presence of the D antigen in primates other than Man, it does not necessarily follow that it is absent from all their tissues because their red cells fail to be agglutinated by the corresponding hæmagglutinin, or even because the red cells fail to absorb the hæmagglutinin. The presence of a hæmagglutinogen in the body though not in the red cells is illustrated in the case of a number of species of monkeys among which there is a reciprocal relation between the presence of the A or B antigen in the saliva and the corresponding agglutinin in the serum. It is certain that a common antigen or similar antigens are present in the red cells of *Macacus rhesus* and of most human beings. In 1933, long before the discovery of the Rh factor as such, Buchbinder claimed to have found such a substance (which he thought to be present in all human beings) which was alcohol soluble and thermostable. These findings with regard to its properties are of interest in relation to the much disputed existence and properties of the Rh hapten.

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Dr. G. Fulton Roberts: Some of these problems might be solved by investigating the variation in degree of antigenicity in red-cell substances. Some red-cell antigens are more potent than others (e.g. D more than C, C more than E). The D^u system shows a variation in antigenic reactivity *in vitro*. Here the various cell samples contain an antigen apparently recognized by the anti-D antibody but the reactions vary in strength, in the number of anti-D sera which are effective, and in reactivity with different types of test employed. Such intragroup variations appear to be constant and heritable. Similar variations in reactivity of cell samples from different animals in one species with an agglutinating antiserum are known.

If it could be shown that such *in vitro* variations were also operative *in vivo* both in terms of immunizing power and of reactivity, it might be possible to account for such anomalies as: (*a*) the discrepancy between incompatible matings and the incidence of the disease, (*b*) not only those mild cases in which the mother is sensitized and the infant unaffected but also the rare but very remarkable cases of healthy incompatible infants born to a mother who had previously delivered several severely affected offspring (unfortunately in none of the published accounts of the latter is the result of the Coombs test given) and (*c*) the observations that transfused cells which become sensitized in some cases survive normally and in other cases are rapidly destroyed.

Section of Endocrinology

President—A. S. PARKES, M.A., Sc.D., F.R.S.

[*November* 23, 1949]

Three cases shown by R. D. LAWRENCE, M.D.

Introduction.—It is well known from experiments on animals that, apart from pancreatic insulin, hormones from other glands play an important part in the total regulation of the blood sugar and the production of experimental diabetes. From these experiments it seems clearly established that:

(1) A centre in the hypothalamus, the area from which nerve impulses flow mainly to the pituitary, has replaced the old puncture centre of Claude Bernard in the floor of the fourth ventricle as the site of puncture diabetes.

(2) From the anterior pituitary itself hormones can be extracted which variously affect carbohydrate metabolism: (*a*) a glycotrophic hormone which, though not itself hyperglycæmic, counteracts insulin hypoglycæmia; (*b*) the adrenocorticotrophic hormone, ACTH, which, through the adrenal cortex, affects carbohydrate metabolism. Its recent use for rheumatoid arthritis has produced a condition like Cushing's syndrome; (*c*) Young's diabetogenic principle from the anterior pituitary which causes permanent diabetes in adult dogs by ultimate destruction of the islets of Langerhans. Perhaps this is closely allied with the growth hormone of Evans which in its purest form also appears to be diabetogenic.

(3) An excess of thyroid hormone empties the liver and the heart of glycogen and promotes a temporary failure to store sugar as glycogen.

(4) The adrenal cortex plays an important part in prolonged blood sugar regulation and the medullary extract adrenaline has a brief but long-established effect in produced brief hyperglycæmia.

When we turn to apply these fairly clear animal experiments to various types of human disease called "diabetes" and characterized by hyperglycæmia many clinical problems remain unintegrated. I have seen—apart from acromegaly, Cushing's syndrome and pheochromatoma — diabetes develop in Fröhlich's syndrome in eunuchism and combined with Addison's disease. Examples of some of these are demonstrated.

I.—Diabetes Mellitus with Obesity and Acromegaly.

Mrs. E. S., aged 53; a housewife with 6 children.

Past history.—She has had no serious illnesses.

Family history of obesity but no diabetes mellitus. Her paternal grandmother weighed 22 st. and a nephew weighs over 20 st.

History of present condition.—Patient was quite normal until after the birth of her last child at the age of 38, at which time she weighed 10 st. 13 lb. Her weight then began to increase and by 1940 had reached 20 st. Her hands and feet were increasing in size and her hats were getting tight. She also began to have headaches. About May 1948 she began to feel thirsty and had some frequency of micturition. She was seen by R. D. L. in July 1948 with symptoms of thirst, frequency, lassitude, genital pruritus and headache.

On examination.—Grossly obese; weight more than 20 st. Her appearance suggested some degree of acromegaly. The skin below the knees was markedly thickened and inelastic. Cardiovascular system: Heart enlarged clinically; B.P.170/100. Examination of respiratory and central nervous systems revealed nothing abnormal. Urine: 3%-4% sugar. Blood sugar at 10 a.m. was 234 mg.%.

Treatment.—Restriction in carbohydrate intake to 80 grammes per day and some restriction in intake of fats. She responded well and three weeks later her urine

contained neither sugar nor ketone bodies, blood sugar was 160 mg.% and thirst and frequency had lessened.

February 1949: The diabetes remained under good control and she had lost over 1 st. in weight. She complained that her feet and hands were still getting bigger.

Investigations.—X-rays: Bones of skull vault and base excessively thickened, hyperostosis very marked in inner tables of frontal bone. Pituitary fossa symmetrically enlarged. Eyes: Presbyopic. No diabetic retinopathy. Discs and vessels normal. Visual fields normal. V.R. less than 6/60, V.L. 3/36.

November 1949: Diabetes under good control; no sugar or acetone in urine. Blood sugar 167 mg.%. Weight more than 20 st. No change in her condition but axillary and pubic hair sparse and fine.

Dr. Raymond Greene: I think that this is a case of Morgagni's syndrome which has previously been reported in association with diabetes mellitus and acromegaly. The complete triad of obesity, hypertrichosis and hyperostosis frontalis interna is present, together with the commonest symptom of headache.

It is difficult to explain the simultaneous occurrence of all these abnormalities. In a similar case of my own the most prominent feature is the headache. Recently Dr. Colin Edwards showed to the Society a patient with hyperostosis frontalis interna who was operated on by Mr. L. C. Oliver (*Proc. R. Soc. Med.*, **43**, 251). He had found the dura attached to the frontal bone in the pits between the bosses and had freed it. The patient had been entirely free from headaches since the operation.

II.—Hæmochromatosis.

Retired schoolmaster, aged 71; married, 4 children.

History.—In August 1937 patient complained of marked lassitude, thirst, frequency and loss of weight, of acute onset. Urine contained sugar. Dr. Lawrence saw him in March 1938. His symptoms were still very marked and he weighed only 9 st. fully clothed. Previous weight 10 st. 5 lb. stripped.

On examination.—Sallow, slaty complexion (this had never been noticed either by the patient himself or relatives) with marked wasting. Axillary hair sparse and wispy as was the pubic hair which was feminine in distribution. Abdomen: Enlargement of liver down to umbilicus, firm and nodular. The cardiovascular and respiratory systems appeared to be normal.

Central nervous system: Some diminution in knee-jerks (jerks only just present with reinforcement). Eyes myopic. Some "dust" in left lens. Urine: Sugar +++. No ketone bodies. Blood sugar 250 mg.%.

Treatment.—He was stabilized on 20 units protamine zinc insulin per day; carbohydrates restricted to 120 grammes per day. Rapid improvement with loss of symptoms and marked gain in weight.

In September 1938 he was taken off insulin and his diet was increased to 150 grammes carbohydrate per day. On this he remained sugar-free until he developed an acute tonsillitis in January 1939 and had to take insulin again. He has remained well and active but has needed a slight and gradual increase in insulin to maintain good diabetic control.

November 1949: Now active and well; appetite good; digestion good. Weight 10 st. 13 lb. (clothed).

On examination.—Slaty pigmentation of skin most marked on face, arms and anterior surface of legs, very little pigmentation of abdomen. Pubic and axillary hair as before. C.V.S.: Hypertension. B.P. 170/95. R.S. normal. C.N.S.: Sensation normal. Arm-jerks present. Knee-jerks ± left and right without reinforcements. Ankle-jerks absent with reinforcement. Plantar reflexes both down. Pulses: Posterior tibial and dorsalis pedis pulses palpable on both sides. Abdomen: Liver edge palpable 3 fingerbreadths beneath costal margin; liver firm; spleen not felt. Eyes as before. Blood sedimentation rate 5 mm. in one hour. Hb 92%.

His diabetes remains well controlled on insulin and restricted carbohydrate diet. He is at present taking a dose of 10 units soluble insulin plus 16 units protamine

zinc insulin daily before breakfast, and his carbohydrate intake is still restricted to 150 grammes per day.

His latest blood sugar was 81 mg.% at 12.35 p.m. His second morning specimen on that day contained neither sugar nor ketone bodies and his night specimen of the day before contained a trace of sugar, but no ketone bodies.

III.—Acromegaly with Diabetes Mellitus and Idiopathic Skin Lesions.

Mrs. E. P., aged 45; married with no children.

History.—1923, at the age of 29, admitted to National Hospital, complaining of increase in weight for one year. Amenorrhœa for two years. Increase in the size of her hands. Alteration in vision for six weeks.

On examination at this time she had a typical acromegalic appearance; her visual fields showed a left temporal hemianopia up to fixation point and in the right eye constriction of the temporal field in the upper quadrant. No other abnormal physical signs. A glucose tolerance test showed:

	Fasting	Hours after 50 grammes glucose
Blood sugar, mg.%:	93	½ hr. 117; 1 hr. 148; 1½ hr. 113; 2 hr. 96

A craniotomy was performed and a tumour which presented to the medial side of the right optic nerve was removed.

Pathological report.—Adenoma of anterior lobe of pituitary the cells of which had abundant cytoplasm with enlarged eosinophil granules, but there were small areas of cells with scanty cytoplasm and without granules which resembled a chromophobe adenoma. The greater majority of the cells were, however, eosinophils. When the patient was seen in December 1933 the visual fields were practically normal.

In 1946 diabetes mellitus was diagnosed on account of moderate symptoms. Treated by some restriction in carbohydrate intake, but no insulin until she was seen by Dr. Lawrence in September 1949.

Present condition.—Typical acromegalic in appearance. Feels well apart from diabetic symptoms and periodic fits of depression. Appetite fair, bowels regular, but has periodic attacks of diarrhœa. Has not menstruated since before operation.

Complains of thirst, frequency, very marked lassitude, slight loss of weight, and skin infection.

On examination.—The cardiovascular and respiratory systems revealed nothing abnormal. B.P. 110/80. Central nervous system: Sensation normal. Knee-jerks both present. Ankle-jerks absent. Plantar reflexes down.

Skin: Numerous white pock-like marks distributed all over the body. The lesions apparently present as vesicles with surrounding erythema. The centre of the lesion becomes blackened and adherent and appears to separate from the surrounding skin at its edges, but then usually becomes infected after which the blackened area separates and healing takes place, leaving a thin white scar. The size of these varies between ¼ in. and 1¼ in.

Diabetes.—When first she was seen she had ++++sugar in both night and morning specimens and the blood sugar was 410 mg.%. She was given a mixed dose of insulin, 20 units soluble plus 20 units protamine zinc insulin, and her carbohydrate intake was restricted to 150 grammes per day. There was no great response to this treatment and the insulin was gradually increased until she was taking 80 units soluble insulin plus 40 units protamine zinc insulin. This reduced her noon blood sugar to 204 mg.%, but she was still passing +++ to ++++ sugar in her urine. Her symptoms improved. Her insulin was stopped for a few days and an insulin depression curve was as follows:

	Fasting	Hours after 20 units soluble insulin I.V.I.
Blood sugar, mg.%:	308	¼ hr. 308; ½ hr. 266; ¾ hr. 250; 1 hr. 230; 1½ hr. 206; 2 hr. 206

Following this she was put on a single dose of soluble insulin 80 units taken before breakfast. Diabetes responded well to this, her noon blood sugar being 132 and the fasting level being 240 mg.%.

Investigations.—B.S.R. 60 mm. per hour: Blood W.R. negative. Hb 88%. Leucocytes 10,500 per c.mm. Culture of pus from skin lesion yielded a heavy growth of *Streptococcus pyogenes*. Catheter specimen of urine yielded a growth of yeasts not of the *Candida albicans* type.

X-ray reports.—Skull: The pituitary fossa is markedly enlarged, and the dorsum sellæ is eroded. A thickened vault, large frontal sinuses and a large mandible make this typical of acromegaly. There has been a right temporal decompression. Feet: The terminal phalanges are markedly tufted and broadened. The bones are thickened and generally roughened with spur formation on the shafts. The ends of the bones are deformed. The changes are more marked in the hands than in the feet. Chest: The straight X-ray of the chest is suspicious of bronchiectasis. No evidence of Koch's infection.

Addison's Disease and Diabetes Mellitus.—S. LEONARD SIMPSON, M.D.

L. X., aged 20; a Naval Officer.

February 1947: Typical Addison's disease developed while serving as an officer in the Royal Navy, aged 18½. Serum sodium 302 mg.%, potassium 31·4 mg.% (very high), chloride 440 mg.%. Kepler test equivocal. X-rays revealed a healed pulmonary apical lesion (father died of pulmonary tuberculosis, aged 37). Blood sedimentation rate normal (3 mm., Westergren). Carbohydrate tolerance almost normal: 115 (fasting), 150, 160, 150, 125, 110 mg.% at half-hour intervals after 50 grammes glucose. Insulin sensitivity normal. Clinical improvement and normal biochemistry on 5 mg. desoxycortone injected daily. Subsequently maintained on an implant of 400 mg. desoxycortone.

June 1947: Weakness, thirst, polyuria; urine contained sugar and acetone. Fasting blood sugar 320 mg.%. Diabetic tolerance curve (200, 310, 350, 400, 380 mg.%). Diabetes controlled by soluble insulin 18 units morning, 16 units evening.

December 1947: 1 gramme salt daily added.

January 17, 1948: Arrived at hospital unconscious in hypoglycæmia, blood sugar 65 mg.%. Serum sodium 306, potassium 25, chloride 676 mg.%. 10 c.c. cortical extract daily. (For full history up to this point *see* S. L. Simpson, *J. clin. Endocr.*, 1949, **9**, 403.)

January 21, 1948: 300 mg. desoxycortone implanted.

February 7, 1948: Patient left hospital well and remained so in 1948. Another desoxycortone implant in October 1948, 400 mg. Changed to globin insulin 24 units daily owing to a tendency to hypoglycæmia.

June 1949: Further implant of 400 mg. desoxycortone; globin insulin now reduced to 14 units.

October 1949: Patient reasonably well but rather apathetic; well-marked pigmentation of gums and inner lip still present.

Comment.—This is 1 of 3 such cases that have come under my personal care. 17 such cases have been recorded with autopsy reports, the adrenal lesion atrophy in 12 and tuberculosis in 5; in all the pancreatic islet cells were reduced in size and stained poorly and there was an increase in connective tissue and lymphocytic infiltration. Diabetes or Addison's disease may appear almost simultaneously or the one may precede or follow the other. Where Addison's disease is superimposed on diabetes mellitus, the insulin requirements progressively fall, e.g. from 70 to 4 units daily as the adrenal insufficiency progressively increases. This adds point to the realization that in ordinary diabetes, the blood sugar concentrations are the result of a balance between subnormal insulin secretion on the one hand and pituitary and adrenal cortex diabetogenic or anti-insulin hormones on the other. since the

insulin requirement of a completely depancreatectomized (for carcinoma of the pancreas) man is in the neighbourhood of 36 units of insulin daily. The variations and instability of blood sugar concentrations in patients suffering from both diabetes and Addison's disease are extreme, even when the daily insulin requirements are small and the insulin sensitivity is great. Similar observations have been made in the case of the Long-Lukens pancreatectomized adrenalectomized animal, which is the experimental counterpart of the clinical condition described above.

Dwarfism, Sexual Infantilism, Diabetes Mellitus and Anæmia.—RAYMOND GREENE, D.M.

Miss J. J., aged 17, the younger of two sisters, the elder being normal.

She first came under observation in 1941, at the age of 8, when she was admitted to hospital in diabetic coma. She had no history of digestive disturbance, diarrhœa or any other serious illness. Nothing more is known of her condition at that time. She was treated with 26 units of protamine zinc insulin and 14 units of soluble insulin once daily, and a diet containing 200 grammes of carbohydrate. On several occasions in the next few years she was readmitted to hospital owing to attempts having been made to control her glycosuria. As she had a low renal threshold this always caused hypoglycæmia. On one occasion she became unstable owing to a severe urinary infection with *B. coli*. In 1945 her weight was 65 lb. and her height 50½ in. Hæmoglobin in July 1947 was 96%, but in October 1947 she was pale and with Hb only 63%. Treatment with iron raised the level to 75%.

She was first seen by R. G. in November 1948, being then just 16 years old. Her height was 52½ in. (upper measurement 27 in., lower measurement 25½ in., span 53⅜ in.) and her weight 65 lb. She had never menstruated. There were no signs of sexual development. Breasts, pubic hair and body hair were absent and the uterus was minute. The skin was soft and like a child's. The abdomen was protuberant and the liver edge could be felt one inch below the costal margin. Anæmia was not suspected and the blood count at that time was not done. Intelligence was good and she was earning her living as a shorthand-typist, but emotionally she was infantile. Her whole appearance and manner suggested a child of 9 or 10. The diabetes was poorly controlled. X-rays showed the bone age to be approximately 14 years. Skiagrams of the skull were normal. The follicle-stimulating hormone excretion could not at that time be measured.

Her diabetes was well controlled by a 14 line Lawrence diet (*see* Lawrence, 1950, The Diabetic Life, London, 14th Ed.) and a daily dose of 48 units of protamine zinc insulin. Thereafter she remained in excellent health for six months. Treatment with stilbœstrol and ethisterone given cyclically produced regular withdrawal bleedings, but there was no sign of breast development, no pubic hair grew and the uterus remained small. The insulin requirements were unaffected. No increase in height. Liver no longer palpable.

In May 1949 she was in her usual health, but when she reported in June she was extremely pale and dyspnœic, with œdema of the ankles, a pink smooth tongue and severe ulceration of the mouth. She had lost 4½ lb. in weight. Investigations showed that her diabetes was still well controlled. Blood count: R.B.C. 2,900,000; Hb 44%; C.I. 0·76; W.B.C. 7,000 (normal proportions). Liver not palpable. Urine normal. Serum proteins 6·5% (alb. 4·8%, glob. 1·7%). Blood urea 21%. Urea clearance normal. Fractional test meal (F.T.M.) normal. Fæcal fats: Soaps 17, free fatty acid 10·2, neutral fats 8·8; total 36 grammes %. She was given iron. A week later a blood count showed: Hb 57%; M.C.H.C. 30%. Corpuscular diameter too various for measurement of M.C.D. with a halometer, but most cells 7·8–8μ. M.C.V. 90 cu.μ. Poikilocytosis and very marked anisocytosis. There was a further improvement in the hæmoglobin level in the next month to 68%, but in the subsequent month no further improvement. Treatment with vitamin B_{12} raised the

hæmoglobin rapidly to 90%; the blood has since remained normal on a fortnightly dose of 20 microgrammes.

With the exception of a period of two months in which she was anæmic, she has been during the past year in excellent health, with her diabetes well controlled. Despite this she has not grown at all and sexual development has not begun.

Dr. Greene suggested that this was a case of ovarian agenesis. He had seen two other cases (one shown last year to the Section and one of Turner's syndrome) in which hypogonadism, dwarfism and diabetes occurred together; and he found it difficult to dismiss the concurrence as fortuitous. He had no explanation to offer of the sudden appearance of what was probably a megaloblastic anæmia.

Dr. I. H. Milner suggested that the diagnosis was a pituitary dysfunction causing dwarfism, anæmia, and even also the diabetes—occurring before puberty—and referred to the series of cases of hypopituitarism with anæmia reported by Groen, Hunter, Snapper and Witts.

Dr. Greene replied that it was usual in anæmia due to pituitary deficiency to find achlorhydria. The patient's F.T.M. was normal. He agreed that without an estimate of the F.S.H. excretion it was impossible to be certain that the ovary was primarily involved. The evidence for a megaloblastic anæmia was poor, but he drew attention to the rapid response to vitamin B_{12}.

Dr. H. Gardiner-Hill thought the whole syndrome might be explained as a case of cryptic idiopathic steatorrhœa with consequent nutritional deficiency.

Dr. Greene agreed that without a fat balance experiment this diagnosis could not be excluded, but pointed out that except for the rather large abdomen there was no positive evidence to support it. There had never been any evidence of vitamin deficiency or of deficiency of any mineral except iron. The F.T.M. was normal and there was no history of digestive disturbance.

Dr. R. D. Lawrence said he thought the whole syndrome could be explained as due to diabetes and that he would expect growth and sexual development to begin now that the diabetes was well controlled.

Dr. Greene pointed out that this condition had been fulfilled for a year without any change during that time.

Dr. Wilfrid Oakley suggested that a liver dysfunction might link the diabetes with the anæmia.

Diabetes Mellitus with Thyrotoxicosis.—I. GILLILAND, M.D., M.R.C.P.

Mrs. A. H., aged 52; housewife, with 3 children.

History.—She was found to be a diabetic during the Civil War in Spain in 1937, and control was inadequate owing to the difficulty of getting insulin. She suffered considerable privations and persecution in Spain subsequent to the Civil War until her escape in February 1948.

Four months after she arrived in this country, where her circumstances were much better than in Spain, she began to suffer from palpitations and sweating, and was nervous and irritable.

When first seen in December 1948, she weighed 5 st. 13 lb. and was obviously diabetic. Fasting blood sugar 220 mg.%. Urine (Benedict) constantly orange. An enlarged thyroid without bruit was noted. She was excitable and had a fine tremor, pulse 100, B.P. 200/100; no abnormal chest signs. She was thought to be a nervous, undernourished and poorly controlled diabetic.

She was fairly well stabilized on 36 units globin insulin and a diet of 2,091 calories, (266 g. carbohydrate, 88 g. protein and 75 g. fat). Gained 10 lb. in eight weeks. However, her nervousness and hyperactive circulation became more obvious with this improvement and her periods, which had been normal, became excessive in April 1949. In May 1949 she was admitted for assessment and treatment of her hyperthyroidism.

Condition on examination before thiouracil therapy: A restless, hyperactive person, with hot moist skin; capillary pulsation present, and a fine tremor. Sleeping pulse 120. B.P. 120/80. Fasting for a B.M.R. estimation precipitated a period of diabetic acidosis. Glucose tolerance test (fasting and half-hourly): 355, 489, 592, 592, 496, 432, 394 mg.% (Fig. 1 (1)). Blood Hb 102%. W.B.C. 8,000; Cholesterol 175 mg.%. Blood urea 42 mg.%. B.M.R. + 64%.

Radioactive iodine urinary excretion (a clearly thyrotoxic result): Hours 0–8: 8·5%; 8–12: 0·3%; 12–24: 0·5%; 24–48: 2·4%. Total 11·7% in forty-eight hours.

Methyl thiouracil 0·2 g. t.d.s. was commenced on 21.5.49 and was followed by a striking improvement. She has had methyl thiour. 0·1 gramme t.d.s. and sod. l-thyroxine 0·2 mg. since June 1949. Has gained 3 st. and her activity is now normal. The diabetes is controlled on P.Z.I. 24 Sol. 10, and a diet of 2,860 calories (carbohydrate 388 g., protein 93 g., fat 104 g.). Pulse 120. B.P. 210/80. Her thyroid has not noticeably increased in size though a great widening of her neck is now evident which her husband states is a return to her normal condition.

Glucose tolerance test at this stage (fasting and half-hourly for three hours): 335, 458, 386, 314, 270, 262 mg.% (*see* Fig. 1 (2)).

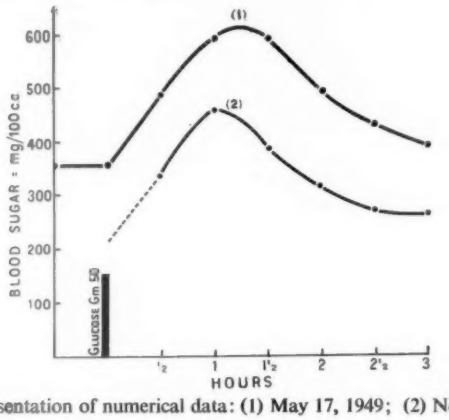


FIG. 1.—Serial presentation of numerical data: (1) May 17, 1949; (2) November 17, 1949.

[*January* 25, 1950]

Hormone Assays on Body Fluids

PRESIDENT'S ADDRESS

By A. S. PARKES, M.A., Sc.D., F.R.S.

I APPRECIATED very much the honour of being elected President of the Section, partly because it really is an honour, and partly because it is, I imagine, somewhat unusual for a biologist to become President of a Section of this Society. I feel, however, that the event has a wider significance than my personal concern. For the last three years, since its beginning in fact, I have been Chairman of the Society for Endocrinology, and the fact that for a brief period the chief offices of both the Section and the Society are occupied by the same person, must be a cause for satisfaction among those who have at heart the progress of endocrinology. The Society and the Section were inaugurated at about the same time, and a minority view that this twin birth was overdoing things has not been substantiated by events. As expected by most of us the two organizations have turned out to be complementary, not conflicting. The Society is concerned mainly with laboratory work relating to vertebrates in general, and in the eyes of a biologist man is just another vertebrate. In these circumstances the Society naturally has a membership consisting largely of biologists and biochemists, though the number of medical members is gratifyingly large. The Section, by contrast, deals mainly with work pertaining to man, laboratory animals coming into the picture largely as tools. Members of the Section could hardly be expected to give their undivided attention to a paper dealing primarily with, say, the plumage of birds, and some members of the Society would certainly feel out of place at a meeting at which patients were shown. There is thus ample room for both of the organizations acting individually within their particular spheres. But I would go further. Not only is there ample scope for both organizations acting independently, there is vital scope for their co-operation. Few

would dispute that two of the best meetings held by either were the two joint meetings held in the last two years. We should look forward, therefore, not only to an increasing emphasis on the individual character of the two organizations, but to an increasing co-operation between them. For this reason I am especially pleased to have been elected President of the Section while still Chairman of the Society. We may hope that one day, not too distant, the Society will return the compliment and elect as its Chairman the President of the Section.

To-day, I want to talk about the estimation and significance of hormones and their derivatives in body fluids, on the one hand to add to our knowledge of the working of the body, and on the other hand as an aid to diagnosis and therapy of disorders of endocrine organs.

I was led to my choice of subject by two considerations. Firstly, of all endocrinological problems, this is the one that most closely brings together the biologist and biochemist with medical men. Secondly, it is one which has been of pressing interest for many years, and promises to continue so. Obviously it would be impossible, or even improper, for me to attempt to give a complete and coherent picture of this vast field. What I want to do is to make a series of rather general points illustrated by discursions into particular matters. My text, if I have one, is "Back to Blood".

Much of what I have to say will sound elementary, but in a complicated problem like this there is much to be said for keeping a firm grasp on fundamental principles. A hormone by its classical definition must appear in effective concentration in the circulating blood. In theory, therefore, it should be possible to find out its normal effective level in the blood, and then proceed to the diagnosis of hypo- or hyper-states according to the levels found in particular cases. This simple idea is obviously subject to easily foreseeable complications. The hormone might circulate in a form in which it is inactive, it might be present in amounts so minute as to be undetectable, it might appear cyclically, or transiently, or variation in sensitivity of the end-organ might be an important factor in determining the effective level in the blood stream. Nevertheless, it is my belief that the key to the problem of effective hormone levels must be sought in the circulating blood. Some of you may remember the work of R. T. Frank in New York, who, twenty-five years ago, immediately following the work of Allen and Doisy, demonstrated the presence of œstrogen (female sex hormone as it was then known) in the circulating blood of woman. Frank and his collaborators followed up this observation with a great deal of work on blood-œstrogen levels under different conditions. Their methods were inadequate to say the least, and they made little impression on the biological or clinical worlds. Looking back, however, Frank's basic idea seems to me to have been right, and he deserves recognition as a pioneer.

Shortly afterwards, œstrogen was discovered in the urine of women and in the blood and urine of men, and then in enormous quantities in the urine of pregnant women. The latter finding was particularly disconcerting, as at that time œstrogen was thought to be connected essentially with the follicular phase of the cycle, and the administration of exogenous œstrogen was already known to terminate pregnancy in certain laboratory animals. These discoveries led to dramatic advances in the chemical field, but confused the biological picture and diverted attention from the circulating blood. The same is true of Zondek and Aschheim's later discovery of large amounts of gonadotrophin in pregnancy urine. In consequence of these diversions, and because of the fact that urine is easier to obtain than blood, by far the greater amount of work on so-called hormone estimations has been carried out on excretion products. This state of affairs is not necessarily very satisfactory, and it can be argued that the discoveries of Zondek and Aschheim, spectacular and valuable as they were, diverted biological thought and research away from the study of the endocrinological integration of normal animals, including man. It is difficult, for instance, to believe that the small amounts of œstrogen found in the urine of the males of many species, and in the urine of stallions in huge amounts, are anything more than an incidental waste

product or bye-product without physiological function in the reproductive processes of the animal itself. The prostate gland, and particularly the uterus masculinus of the stallion show no sign of œstrogenization. Moreover, there is good reason to believe that different hormones may have similar excretion products, while others have no excretion product at present recognizable as such. The diagnostic and biological significance of hormone assays on urine must, therefore, be considered in the light of all these complications. I am not competent to speak of clinical matters, but in laboratory work one has constantly to be on guard lest a routine procedure degenerate into a mere ritual.

In saying this, I must not give the impression that work on the hormones of the circulating blood is negligible. There is, for instance, a good deal of information about the blood concentration of œstrogen and gonadotrophin during normal human pregnancy. Estimations of this kind are inherently more difficult on the non-pregnant subject because of the small amounts of material involved, and much of the work carried out on the levels of reproductive hormones during the menstrual cycle is for the most part not very convincing. The difficulties are largely those of technique. Blood samples must be strictly limited in amount; and, at best, they contain only small amounts of active substance in a highly complex medium. In the circumstances the problem turns on precision of extraction where this is attempted, and on the sensitivity and specificity of the chemical or biological assay method. It is most significant to note that important advances have recently been made on all these fronts, and that in general a back-to-blood movement is gathering momentum. It is encouraging to see that chemical methods for the estimation of steroids, especially progesterone, in blood have recently been worked on by Butt, Morris and Morris (1949), and it may be recalled that Reynolds and Ginsburg in 1942 made an early investigation of this field. It is to be hoped that further attention will be given to this problem. Of all the hormones of interest to the student of the reproductive processes, progesterone has been the most elusive in body fluids. This fact is due to the comparatively large amounts required for the usual biological test and to its apparent absence from urine at all stages of the reproductive cycle. In consequence, a great deal of attention has been given to the inactive excretion product of progesterone, pregnanediol, which has become one of the most investigated of all urinary steroids. The estimation of pregnanediol as an indication of luteal function has two serious disadvantages: it is difficult to measure in small amounts, and it may be derived from other sources than progesterone. I am sure that many of those actively concerned in this work, including my very old friend and collaborator Professor G. F. Marrian, will agree if I say that much of the work would not have been carried out had there been available a simple method of estimating progesterone in circulating blood.

Biological methods, about which I am more competent to talk, are also being improved. It is the general rule that methods based on local application of the active substance to the responding tissue are much more sensitive than those depending on systemic application. The injection of prolactin into the wall of the pigeon crop, the inunction of androgen to the capon comb, and the intravaginal administration of œstrogen, all provide illustrations to this general rule. Local administration also has the advantage that it distinguishes between immediately active substances and those which require modification in the body before becoming active. Thus, Emmens separated synthetic œstrogens into two categories, real œstrogens and pro-œstrogens which were activated in the body. By means of intravaginal assay, Markee and Berg (1944) were able to study the blood concentration of œstrogen during the normal menstrual cycle. Their results were concordant with, but better defined than those of Fluhmann and others, and showed a much increased concentration of œstrogen about the time of ovulation and during the first part of the luteal phase. It is to be supposed that many, or even most, of Markee and Berg's subjects were having normal ovular cycles, and the results imply that œstrogen withdrawal is a factor in the initiation

of menstruation even in the presence of a corpus luteum. In anovular cycles it may well, of course, be the chief factor. We may look forward to further progress, especially along the lines of the work of Szego and Roberts (1946, 1947) who found that in normal and pregnant cows, normal and gonadotrophinized rabbits, and in pregnant women, the blood œstrogen was in two forms, free and protein-bound, in the ratio of about one-third and two-thirds respectively.

Pursuing further this matter of the biological assay of hormones in circulating blood, we come again to progesterone. I have referred a few minutes ago to the difficulties of estimating this hormone in body fluids, and it is encouraging to be able to point out a very substantial advance on the biological side in the last two or three years, and to provide another example of the value of local administration in assay work. Local administration is obviously most easy where the organ in question is accessible from the exterior of the animal. It is, therefore, more difficult to evolve such a method for progesterone, which gives specific response only in the uterus. However, McGinty, Anderson and McCullough (1939) found that the uterus of the œstrogen-sensitized rabbit responded typically to minute amounts of crystalline progesterone (0·0005–0·005 mg.) placed directly into the lumen. This was confirmed by Haskins (1939) who further found that a positive reaction could be obtained in such a test by 0·2 c.c. of serum from a pregnant guinea-pig. The most interesting work of this kind, however, is being developed by Hooker and Forbes in Yale. These authors have evolved a microbiological test for progesterone which depends on the local administration of progesterone or the material for test, into the lumen of an isolated segment of the uterus of the ovariectomized mouse. A positive reaction is indicated by characteristic changes in the stromal nuclei of the endometrium. The sensitivity of the test is such that the minimum effective dose of progesterone is 0·0002 μg., one five-millionth of a milligramme (Hooker and Forbes, 1947). The sensitivity is remarkable when it is considered that about 0·5 mg. is required for the standard Corner test, or the deciduoma reaction in the rat. The Hooker-Forbes test for progesterone must, in fact, rank high among the most sensitive biological tests. The test, moreover, is highly specific (Hooker and Forbes, 1949*b*), a wide range of biologically active and inactive steroids having been found to give negative results. Of the substances tested only pregnanediol in a dose 30,000 times greater than that of progesterone gave a dubious positive response. The test has certain disadvantages; it is time-consuming, and the end-point of the reaction is not very sharp. These, however, are administrative difficulties rather than biological ones. By the use of this test, Hooker and Forbes (1949*a*) found blood progesterone levels of between 4·0 and 8·0 μg. per ml. of whole blood during phases of luteal activity in rabbits, mice, a monkey, and an 8 weeks' pregnant woman. All the active material was in the plasma, 90% being free and 10% protein-bound, fractionation being accomplished by the methods employed for blood œstrogen by Szego and Roberts (1947). The free/bound ratio appears to be different from that found for œstrogen, since over 60% of blood œstrogen is found in combination with protein. Hooker and Forbes consider that protein binding is a means of hepatic inactivation of progesterone in mice. Incidentally, it would be interesting to know whether humans suffering from liver damage show signs of hyper-progesteronism in the same way as they are said to show signs of hyper-œstrogenization. The fruits of the work of Hooker and Forbes are only just beginning to appear and we may look forward confidently to further interesting results. In the meantime we may note that variation in blood progesterone levels have been noted during the laying cycle in domestic fowl. As is usual in this kind of work, Fraps, Hooker and Forbes (1949) have since recorded the occurrence of comparatively large amounts of progesterone in the blood of cockerels, an intellectual dilemma reminiscent of that caused by the discovery of lactogenic hormone in the pituitary of fishes.

I come now to my last point. There has recently been much discussion as to the best way of arranging for and organizing work on hormones and their derivatives in

human body fluids, and I want to summarize some general considerations as they appear to me. In doing so I must say immediately that I have had the benefit of discussions with various members of the Section who are actively interested in the matter, notably Dr. A. C. Crooke, Professor C. H. Gray, Dr. E. F. Scowen, Dr. Russell Fraser and Professor G. F. Marrian.

Let us consider first the pros and cons of a central assay laboratory, as a common facility for hospitals, and having no control or power of selection of material sent in. If it could be made to work such an organization would have certain advantages, standardization of methods, concentration of equipment and personnel, &c., but the disadvantages are overwhelming. It could deal with little but routine work and might well be swamped under a mass of indifferent material. It would probably degenerate into a slot machine, which would be demoralizing for staff and clients alike. Worst of all, however, it would do nothing to foster the contact between clinicians and laboratory workers which is necessary if they are to appreciate each other's problems and limitations. On balance, I feel strongly against any attempt to set up such a central laboratory.

Dealing now with organizations designed to advance knowledge, as well as to carry out a certain amount of routine work, I think one must be quite clear as to the objective in view. In other words, one must be clear as to whether the aim is to advance knowledge along whatever promising line may emerge, or to advance knowledge in some particular direction, for example, in a clinical direction. For some three years before the war there was a small unit consisting of two biochemists and a biologist working at Hampstead. The immediate object of this unit was to tidy up, biologically and biochemically, what appeared from the literature to be a very untidy situation. To produce quickly knowledge of immediate clinical usefulness was a minor object. Experience with this unit showed some of the inherent difficulties; one had constantly to beware of the temptation, or even the pressure, to fritter away time and resources in all kinds of side issues and odd assays. This unit, in a somewhat isolated Institute devoted entirely to research was, of course, largely dependent for the supply of material on the good nature and helpfulness of clinicians to whom we could offer little in return. At the end of three years' intensive work we were still unable to tell with certainty whether any particular sample of urine had come from a man or a woman. The unit, however, did much fundamental work, the main conclusions of which were summarized by Dr. Callow to this Society in 1940. The chief result of immediate clinical usefulness was the recognition of isodehydroandrosterone as the source of the extraordinary androgenic activity of the urine in certain types of adrenal tumour, and the application of this finding to diagnosis, by Crooke and Callow (1939).

For the purposes for which it was started the unit at Hampstead was well situated. Where, however, the main object is the advancement of knowledge in a clinically useful direction, I feel sure that the biochemists and biologists must be in close touch with the clinicians; in other words the laboratory workers must be brought to the clinical material, not the material to the laboratory workers. There are, at present, several hospitals in which biochemists and biologists are working in the closest collaboration with clinicians on endocrinological problems, whether or not the organization actually has the title of an endocrine unit. This seems to me to be a satisfactory state of affairs and one which should be pursued to the limit of its usefulness. What this limit is, namely what is the optimal concentration of endocrine units, I am not in a position to say. It is, however, easy to see that every unit cannot be all-embracing. The range of facilities required for a complete organization is steadily increasing, and now includes biological tests for androgens, œstrogens, progesterone, corticoids, gonadotrophins, thyrotrophins, adrenocorticotrophins, and others; and on the chemical and physical side, tests for 3-, 17- and 20- ketosteroids, œstrogens, pregnanediol, and others, as well as measurements of radio-activity and many ordinary biochemical tests. All this implies great elaboration of staff and equipment. And the

requirements are constantly increasing. Allow me to quote from a review by Dobriner (1948), of the work carried out by him and his colleagues at the Sloane Kettering Institute for Cancer Research, New York, on the steroids of human urine, with special reference to substances possibly indicative of early cancer:

"The steroids, after hydrolysis of the conjugates, have been separated into several fractions and we have examined thus far in detail the α- and β-ketones. Up to the present time we have been able to isolate over 45 steroids from these fractions. Since these steroids are closely related chemically and differ but little in their properties, we found it necessary to employ a physico-chemical method of separation. This technique, chromatographic adsorption analysis . . .

"When very closely related substances are present 'fractional chromatographic analysis' is necessary. This involves several chromatograms. The procedure is reminiscent of a systematic fractional crystallization, but is far more efficient, especially with respect to recovery of material. When applied to the α-ketonic fraction from a single specimen of urine, these procedures result in the accumulation of from 500 to 3,000 separate fractions, from which the individual steroids are obtained. A quantitative measure of these constituents is achieved by application of the Zimmermann reaction. Each individual steroid is then isolated and characterized in the usual way by determination of melting point, specific rotation, and, as will be discussed below, its infra-red absorption spectrum. Confirmation of the structure of the compound is obtained by the preparation and characterization of suitable derivatives. Wherever possible, the substance isolated has been compared with an authentic sample.

"In the course of this study a total of 42 apparently homogeneous and non-identical substances have been encountered. 26 of these have been fully characterized and identified; the other 16 are characterized and are probably new ketosteroids. 11 of the fully identified compounds have been isolated from urine by previous investigators; thus, 31 fully or partially characterized substances have not been encountered previously in human urine."

Dobriner's laboratory is enormously impressive, and obviously he and his colleagues are obtaining information of the greatest scientific interest. Whether it is of equal clinical importance I do not know. My point is that a set-up of this kind cannot be expected in every endocrine unit, and the same applies in a lesser degree to other complicated physical and chemical apparatus. For this, and other reasons, it seems that each unit, apart from carrying on whatever amount of routine work may be thought desirable and possible, should select and concentrate on a small number of problems for intensive investigation. This idea, which is already largely being acted upon, implies that there should be close contact and consultation between the various units, so that the total resources may be brought to bear in the most effective manner. Consultation is also desirable for the standardization of routine methods which, due to constant slight modifications which are not necessarily improvements, tend to get inco-ordinated and to complicate the comparison of results. I incline to the view, therefore, that if any central body such as the Medical Research Council is to take a general interest in this matter it should be on the lines of supporting individual units and facilitating their mutual co-ordination, rather than on the lines of providing a central laboratory for routine assays. And, I hope that any such body will take as its maxim "Back to Blood".

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Section of Anæsthetics

President—GEOFFREY ORGANE, M.D., F.F.A.R.C.S.

[*December* 2, 1949]

Males and Females as Anæsthetic Risks

By TORSTEN GORDH, M.D. (*Stockholm*)

THIS is a statistical analysis of personally conducted anæsthesias in cases of gall-bladder surgery and gastric resections during the five-year period 1944/48. The material comes from the University hospitals (Karolinska Sjukhuset and Serafimerlasarettet) and private clinics in Stockholm. It is thus strictly personal material from the anæsthetic point of view, and from the surgical side it deals with well-defined groups of operations, where both indications and technique have been uniform. It includes most of the serious cases at the hospitals, and the average age is exceptionally high, since the worst risks and the oldest patients have been handled by the most experienced anæsthetist. The operations were performed by experienced surgeons : 80% by professors in surgery, 15% by assistant professors and 5% by residents.

The anæsthetic record card introduced by Nosworthy and modified according to local requirements was used for the purposes of this study. The judgment of the pre-operative risk, the choice and conduct of anæsthesia and the post-operative follow-up have been made by the author in every case and with the idea of a later statistical investigation.

428 *cholecystectomies* (Tables I–V).

In these tables the incidence of post-operative pulmonary complications is shown to give a general view of the post-operative course. Both minor and major complications are

TABLE I.—CHOLECYSTECTOMY (428 CASES)

Pathological condition	Operation performed	Total cases	Deaths	Mortality %
Cholecystitis and cholelithiasis	Cholecystectomy with or without cholangiography, or exploration of the common bile duct	351	5	1·4
Cholecystitis	Cholecystostomy	4	0	0
Cholecystitis complicated by stones in the common bile duct with or without jaundice	Cholecystectomy + choledochotomy with or without cholangiography or choledochostomy	54	1	1·8
Stones in the common bile duct recurring after, or overlooked at, a previous cholecystectomy	Choledochotomy with or without choledochostomy	19	0	0
		428	6	1·4

included, and were as follows : cough (6), bronchitis (6), atelectasis (3), bronchopneumonia (12) and pleuritis (1). Table II shows the age distribution. The majority, 61%, are over 50 years of age. The differences in pulmonary complications are not statistically significant for any age.

TABLE II.—AGE DISTRIBUTION

Age	Total cases	Post-operative pulmonary complications %	Deaths	Mortality %
21–30	32	0	0	0
31–40	43	2·3	0	0
41–50	89	2·2	0	0
51–60	132	8·3	2	1·5
61–70	104	10·6	4	3·8
71–80	28	3·5	0	0
	428			

TABLE III.—PHYSICAL STATE

Risk	Total cases	Post-operative pulmonary complications %	Post-operative circ. complications %	Deaths	Mortality %
I	98	2·0	2·0	0	0
II	228	6·1	2·7	2	0·8
III	93	9·6	8·9	3	3·2
IV	9	11·1	22·2	1	11·1
	428				

Table III shows the distribution according to the patient's physical condition. The grading is based on the physical state and the usual four-risk grouping is used. In judging post-operative results a more accurate view is obtained by grading the patients by physical state or risk. A qualitative presentation also gives more information than a purely quantitative one, as in Table I. Providing the anæsthesia and operation are " lege artis " performed there ought to be no mortality in risk I, whereas a mortality of 20% in risk IV may be considered reasonably normal.

TABLE IV.—ANÆSTHESIA

Anæsthetics: Primary and secondary	Total cases	Complications during anæsthesia: Resp. %	Circ. %	G.–I. %	Post-operative resp. complications %	Deaths	Mortality %
Spinal + + i.v (230) + N_2O (130)	236	2·1	34·2	7·6	5·5	5	2·1
Intravenous + + N_2O (152) + local (155) + curare (127) + C_3H_6 (20)	169	20·6	17·1	0·6	7·1	1	0·5
Ether	23	8·7	26·0	8·7	4·3	0	0
	428						

The material is presented according to anæsthetic used in Table IV. Spinal anæsthesia was the primary method in 55% and intravenous anæsthesia in 40%. Ether was used in only 5%. The complementary secondary anæsthetics are recorded in the table. A special study of the course of anæsthesia showed that only 60% were considered satisfactory. Exacting criteria have been used and all deviations from the normal physiological state have been recorded. Complications occurred mainly from the respiratory, circulatory, and gastro-intestinal systems. The main *respiratory* ones were laryngospasm, bronchospasm, obstructed airway from other causes, and respiratory arrest. These were most common with intravenous anæsthesia, 20·6% against 2·1% with spinal anæsthesia. The *circulatory*

complications were respectively 17·1% and 34·2%, being most common with spinal anæsthesia. They were noted as severe fall in blood pressure (to 70 mm.Hg or below), tachycardia, and arrhythmia. *Gastro-intestinal* troubles such as vomiting, hiccough and nausea were also commoner during spinal anæsthesia, the frequencies being respectively 7·6% and 0·6%, a difference which is statistically significant, as calculated by ordinary formulæ.

However, all complications during anæsthesia and operation have been treated promptly, so that the patients have left the operating theatre in the most satisfactory condition possible, as assessed by the presence of reflexes and by adequate respiration and circulation. 92% of the patients have been so wide awake that they have reacted or replied to questioning. The duration of anæsthesia and operation has accordingly not influenced the end-results in any significant way, as will be observed in Table V.

TABLE V.—DURATION OF ANÆSTHESIA AND OPERATION

Anæsthesia Time in hours	Total cases	Post-operative resp. complications %	Deaths	Mortality %
$<\frac{1}{2}$	11	9·1	0	0
$\frac{1}{2}$–1	219	6·4	3	1·3
1 –$1\frac{1}{2}$	136	5·1	3	2·2
$1\frac{1}{2}$–2	51	8·0	0	0
2 –3	11	9·1	0	0
	428			

222 *gastric resections* (Tables VI–X)

The analysis of the gastric resections is presented in exactly the same manner and in the same sequence as for the cholecystectomies. The same type of resection was performed in all the 222 cases. The post-operative *pulmonary complications* in this series amount to 13·5% and were as follows : cough (8), bronchitis (6), atelectasis (1), bronchopneumonia (14), pleuritis (1). The circulatory complications amounted to 7·2% and were noted as : severe fall in blood pressure, shock (5), internal hæmorrhage (3), thrombosis (3), pulmonary emboli (4), heart failure (1). The pathological conditions for which the operation was performed and the mortality are give in Table VI. Table VII gives the age incidence and shows that the majority of patients (53%) were over 50 years of age. In the main, the same comments may be made here as for the first group.

TABLE VI.—GASTRIC RESECTION (222 CASES)

Pathological condition	Operation performed	Total	Deaths	%
Gastric or duodenal ulcer	Gastric resection (Billroth II)	173	6	3·4
Gastric or duodenal ulcer with acute hæmorrhage		8	0	0
Post-operative jejunal ulcer		3	0	0
Perforated gastric or duodenal ulcer		6	0	0
Carcinoma		32	2	6·2
		222	8	3·6

TABLE VII.—AGE DISTRIBUTION

Age years	Total cases	Post-operative pulmonary complications %	Post-operative circ. complications %	Mortality %
20–30	16	6·2	0	0
31–40	33	9·0	15·1	2·9
41–50	58	15·4	8·6	1·7
51–60	58	8·6	3·4	5·6
61–70	45	17·4	4·3	2·2
71–80	12	0	8·3	4·1
	222			

TABLE VIII.—PHYSICAL STATE

Risk	Total cases	Post-operative pulmonary complications %	Post-operative circ. complications %	Deaths	Mortality %
I	57	11·9	5·9	0	0
II	118	11·1	8·3	3	2·8
III	38	12·0	5·1	3	7·6
IV	9	11·1	11·1	2	22·2
	222				

TABLE IX.—ANÆSTHESIA

Anæsthesia: Primary and secondary	Total cases	Complications during anæsthesia: Resp. %	Circ. %	G.–I. %	Post-op. resp. compl. %	Post-op. circ. compl. %	Deaths	Mortality %
Spinal + + i.v. (168) + N_2O (75) + ether (4)	169	2·9	25·5	29·5	14·1	7·6	7	4·1
Intravenous + + N_2O (48) + local (46) + curare (42) + C_3H_6 (3) + ether (4)	53	18·8	22·6	7·5	11·3	5·6	1	1·9
	222							

TABLE X.—DURATION OF ANÆSTHESIA AND OPERATION

Anæsthesia Time in hours	Total cases	Post-operative resp. complications %	Post-operative circ. complications %	Deaths	Mortality %
1	7	28·5	0	0	0
1 –1½	63	14·3	7·8	4	6·3
1½–2	90	10·0	6·6	3	3·3
2 –3	53	9·4	9·4	1	1·9
3 –4	9	22·2	0	0	0
	222				

Sex differences in the material (Table XI, Groups A and B).

The main causes of death in both series were : paralytic ileus (5), pulmonary emboli (2), peritonitis (3), hepato-renal syndrome (1), heart failure (1), bronchopneumonia (1), cachexia (1). The fact that all the deaths occurred in males prompted me to make a comparison of the behaviour of the sexes. Table XI shows some of the findings.

TABLE XI

Sex	Total cases	%	Average age	Average risk	Anesth. period satisfactory	Post-op. complications: Resp.	Circ.	G.–I.	Deaths	Mortality %
GROUP A.—428 CHOLECYSTECTOMIES										
M.	130	31	61	2·2	50%	11·5%	7·0%	14%	6	4·6
F.	298	69	56	1·9	65%	3·6%	3·0%	19%	0	0
GROUP B.—222 GASTRIC RESECTIONS										
M.	162	73	56	1·9	46%	15·4%	8·0%	11·1%	8	4·9
F.	60	37	54	2·2	65%	8·3%	5·0%	21·1%	0	0

In Group A, the cholecystectomies, the female sex predominates with 69%, and in Group B, the gastric resections, the male predominates with 73%. These figures are in accordance with those of other observers. But in spite of this difference the behaviour during and after

anæsthesia and operation is strikingly similar for both sexes. There are no statistical significant differences as to post-operative complications and mortality in the different age groups. The average risk varies in both groups. In Group A, the average risk for males is higher than for females, and in Group B, the opposite is observed.

If we look at the course of the anæsthesia we find that whereas for females 65% of the anæsthetics have been considered satisfactory, only 46% and 50% in the male cases have been so. We know that men are more resistant to poisons and to drugs in general, owing to their more vigorous constitution. In any case, in this material there is a statistically significant difference in the frequency of complications during anæsthesia.

As far as the post-operative pulmonary complications are concerned the difference is well known and is also statistically very evident. King found in his classical work in 1933 that the incidence of pulmonary complications among men was at least twice that among women. He designated as " bad risks " men having operations on the stomach and duodenum, gall-bladder and intestines owing to the consistently high percentage of pulmonary complications in such cases. Brock finds the same in his study in *Guy's Hospital Reports* (1936). Holmes found in his analysis of pulmonary complications in 2,064 consecutive cases (1948) that the majority of complications occurred in men. The heavier smoking by men is one explanation ; another is that in women the respiration is predominantly costal in type, so that an abdominal wound produces less reduction of respiratory exchange.

It is also a well-known fact that women are more sensitive to morphine and its derivatives than men, which accounts for the finding of a higher incidence of post-operative *vomiting* and *nausea* among women. However, the more serious complications are more frequent in men. Thus, of the 13 cases with *paralytic ileus* 11 were men, 5 of whom died of paralytic ileus. In 12 cases with hiccough there was only 1 woman. This tendency to hiccough in males is also noted during the actual operation.

It appears from this analysis that males are a poor risk in general, and are more liable to anæsthetic and post-operative complications, a fact which does not seem to be generally recognized. However, vital statistics show that the average expectation of life for a woman in the U.S.A. is five years longer than for a male. Investigations by Johnstone and Hosker (1948) show a higher mortality among males of all ages from pneumonia, bronchitis, appendicitis, peptic ulcer, &c. They conclude that the occupational differences must be an important factor in producing dissimilarity of male and female death-rates.

Allen (1934) states that " mere maleness influences unfavourably the resistance of the organism to disease at all ages". Hamilton (1948) points out that the shorter life span of males characterizes most of the species of animals so far investigated, i.e. 42 species including nematodes, molluscs, birds, insects, fish and mammals. This shows the error of assuming that the differences in modes of life and habits are a factor in the different longevity of males and females. Supported by experiments on animals and human castrates he proves that testicular secretions contribute to the lesser viability of males. In addition to specific actions upon the reproductive organs, testicular secretions increase metabolism and exert widespread effects throughout the body.

It is suggested that androgens, particularly those derived from the testes, contribute to the vulnerability of males, from the medical viewpoint, by this increase in the rate of metabolism, which also results in shortening the life span. In brief, Hamilton says, a price is paid for a beard and the presence of functioning testes. There may be something in this, and possibly the greater vulnerability and higher mortality among males subjected to anæsthesia and surgery are another aspect of this biological phenomenon.

In past years a certain mortality after anæsthesia and surgery was taken for granted. Nowadays, with modern methods and a steadily decreasing mortality, we search for causes in every fatal case and for explanation of variation in the incidence of these mishaps.

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Clinical Science Applied to the Problems of Anæsthesia

By R. P. Harbord, M.D., F.F.A. R.C.S.

"If you consider the successive systems of Philosophy ; if you free yourself from the influence of persuasive rhetoric, intricate logic and ancient authority ; if you delve far down beneath the surface—what will you find, more often than not, but assumptions, which everyone is as free to deny as to accept ; followed by speculation and assertion, without proof ?"

These words of Lord Samuel's (1947) can be applied to our problems. Are we satisfied with the foundations of our own teaching ? Are not some of them based on assumptions ? In his Presidential Address to the Section of Experimental Medicine & Therapeutics, a little over a year ago, Professor Pickering (1949) pointed to examples of ineffective though time-honoured treatment based on assumptions.

The considerable advances made by Sir James Mackenzie in making sound the structure of cardiology show something of what can be achieved by a study at the bedside—bedside science. Sir Thomas Lewis (1935) has defined Clinical Science as : "The branch of knowledge that centres upon human beings, but which also includes directly relevant parts of allied sciences."

Hindrances to the study of man and his ills have been exposed by Wilfred Trotter (1941) who wrote :

"The observer must wait upon the natural occurrence of the phenomena he wishes to study. The phenomena may be too infrequent for their significant recurrence to come within the span of life, they may be too complex and too closely mixed with irrelevant events for the invariable sequences they possess to be detected."

Continuing in a more hopeful vein he wrote : "Science has found a means of escape from the limitation of the method of observation in the method of experiment."

Because of the spate of new drugs, all of which are potentially dangerous, and new methods, due to recent changes in the practice of anæsthesia, there is, at the present time, a real need for much careful investigation to determine what happens to patients during surgical operations.

The significance of data found during miscellaneous operations is difficult, if not impossible, to understand. Much more can be learnt by studying a group of patients undergoing the same operation, and further study of allied operations may yield additional information. By such means the results of natural experiments may be revealed.

The Making of Observations

Julian Taylor (1949) has written : "Accurate observation followed by accurate thought is a straighter route of progress and less encumbered, than the collection of figures, especially other people's, the so-called statistical method."

In making observations I have not used a special form. The essential is to record as much as possible which may be useful at some later date and which is documented so as to be intelligible. Essentials are not easy to foresee during the early stages of an investigation but, with the passage of time, the very problems that arise themselves suggest the means for their solution when possible. Impressions are of value as guiding lights : they act as a mental stimulus.

There is not enough room on what is now the standard anæsthetic record card. I refer to the special punched card system which I can only use for original data that is simple and requires no qualification. By "simple" I mean that which can be fully expressed in one or at most two or three words like "cuffed endotracheal tube", which can be encircled on a printed form, and leaves no room for doubt at a later stage. On the other hand phrases like "minor respiratory complications", "bronchitis", or "respiratory obstruction" may mean little or much or even vary in significance with different people. One would want to know precisely what was meant, or for how long the state of affairs lasted, and there is no space on the standard cards for this information.

Notes on the Observations Made in an Investigation of Anæsthesia for Rectal Operations

All the observations were personally recorded at the time of their occurrence both before, during and after the operations. The notes run into several pages for operation alone and

by the time the patient leaves hospital a small monograph has been made mainly on plain sheets with one or two columns only for repetitive type of data. In such a record there should be clearly stated all the evidence in support of a diagnosis such as "bronchitis". If records could be made on these lines by disinterested but enthusiastic observers many of the phenomena which normally appear within the single span of life could be compared.

When a few records of the kind indicated above have been made it requires a feat of memory to carry in one's head more than a fraction of the findings. The system I use is as follows :

The data are sorted on to summaries each of which has a number of coloured signals to represent important points. The summaries are specially mounted so that the signals are all visible thus conveying the predominating features at a glance as the investigation proceeds. The order of the summaries on the base mount can be readily altered which is of great value when classifying data.

The rapidity with which events occur at operation prevents one person from administering the anæsthetic and making a full record at the same time. Practically all the anæsthetics were given by the consultant anæsthetists of the Leeds United Hospitals who have co-operated fully with me.

Time has been expressed in minutes from the beginning of analgesia or anæsthesia, whichever came first. When the interval between observations exceeded 15 minutes after operation this was taken as the end of the period of continuous observation.

Blood loss at operation is an important consideration. If known quantities ($\frac{1}{4}$, $\frac{1}{2}$, $\frac{3}{4}$, 1, $1\frac{1}{4}$, $1\frac{1}{2}$ pints) of blood are spilled on to swabs and towels a good idea can be gained with a little practice of the amounts lost at operation. The estimate of blood loss obtained in this way, which I have termed the *clinical estimate*, compares well with the results gained in the same cases by an independent person, using a photo-electric method for measuring hæmoglobin on the swabs. To calculate the amount of blood one has also to know the patient's mean hæmoglobin. All the estimates were clinical in this investigation (*see* Table I).

TABLE I.—COMPARISON OF THE RESULTS OF BLOOD LOSS ESTIMATION ON SWABS AND TOWELS DURING MAJOR LIMB OPERATIONS (CUP-ARTHROPLASTY), BY A PHOTO-ELECTRIC METHOD OF MEASURING HÆMOGLOBIN, AND THE CLINICAL ESTIMATE MADE BEFOREHAND

Case reference	Blood loss estimates (in pints)	
	Clinical estimate	Photo-electric method
D.4b	$1\frac{1}{4}$	1·31
D.5a	2	1·64
D.6	$1\frac{1}{2}$	1·79
D.8	2	1·45
D.9	2	2·33
D.10	$1\frac{1}{4}$–$1\frac{1}{2}$	1·12

PREVIOUS WORK ON CASES WITH CANCER OF THE RECTUM

J. A. Lee (1947) states that there is often *considerable shock* produced in the abdomino-perineal resection of the rectum.

Frankis Evans (1947) believes that shock is largely proportional to *blood loss* in operations for cancer of the rectum. He has stressed the magnitude of the operation and also that the time factor has to be considered from the point of view of hæmorrhage.

Wilkinson (1942), referring to the perineal stage of the abdomino-perineal operation states that, "it is at this time, when the maximum effect of most spinal anæsthetic agents has been passed and the anæsthetic action is on the wane, that the patient exhibits shock most frequently".

Gabriel (1934) considers that the chief risks of the abdomino-perineal excision of the rectum are sepsis and shock. He states that: "*Shock*, most surgeons will agree, supervenes in the latter stages of the operation, particularly when the patient is turned over into the left or right lateral position, and during the final perineal excision."

Jarman (1947) states that there is a very marked fall in B.P. *when the patient is turned on to his side* for the perineal part of the operation and sometimes the B.P. cannot be recorded. Hasler (1933) states that: "For excision of the rectum spinal anæsthesia is invaluable as a means of preventing shock." Loftus Dale (1947) stated that he had abandoned spinals in favour of curare *thereby avoiding* the fall in B.P. which accompanies the *movement* of a patient from the Trendelenburg to the lateral position under spinal.

Lloyd-Davies (1947) has again stressed the magnitude of the operation and has stated that one of the most important precautions to take is the *control of the B.P.* He further stated that the *turning of the patient* during operation lowers B.P. very considerably and on occasions to dangerous levels. He therefore recommended the lithotomy-Trendelenburg position. This simultaneously exposes the abdominal and perineal fields and makes possible the synchronous combined abdomino-perineal resection, and he claims that shock is thereby minimized.

Gabriel and Wilkinson refer to shock at the perineal stage; Jarman, Loftus Dale and Lloyd-Davies refer to a fall in the B.P. on turning the patient. By "shock" do these observers mean a fall in B.P.?

Thus the following require investigation: (1) Blood loss and the duration of operation from this viewpoint; (2) change of position under anæsthesia; (3) the control of B.P.; (4) what is a dangerous level of B.P.?

I chose to watch operations on patients with cancer of the rectum because there are a number of different ways of removing the growths. I thought that a comparison might produce valuable information on the effects of surgical trauma as distinct from postural changes for there is no change of position during the perineal stage of the synchronous combined operation. These are severe operations in people in late middle or old age. I also wanted to demonstrate what is meant by "deterioration" at operation.

Observations on Cases with Cancer of the Rectum

Operative procedures.—This is a small series of 83 operations. 52 were synchronous combined abdomino-perineal resections; 19 were laparotomies without further procedure or else a palliative colostomy was carried out. One abdominal resection of the colon is included amongst this group. There were 6 perineal resections of the rectum following colostomy at a previous date, 1 abdomino-perineal resection and 5 perineo-abdominal resections.

The synchronous combined abdomino-perineal resection.—The patients were unselected. There were 33 males and 19 females. The ages ranged from 27 to 83 years, the majority being between 51 and 70 years. 7 were aged 70 years or more.

The methods of anæsthesia can be divided into two main groups: (1) intravenous barbiturate (thiopentone), *d*-tubocurarine chloride, and inhalation (nitrous oxide and oxygen; cyclopropane in only 3 cases) by the CO_2 absorption method. I shall refer to this group as the barbiturate and inhalation group, which comprised 20 cases; (2) spinal (nupercaine 1 : 200 or 1 : 1,500) with intravenous barbiturate (mainly kemithal) but without inhalation. I shall refer to this as the spinal and barbiturate without inhalation group, which comprised 21 cases.

Four cases had spinal analgesia alone; 7 had a spinal and intravenous barbiturate and inhalation.

Eight patients died; 2 within three hours of the end of operation, the remainder at intervals of from two to forty-two days after operation. It is not possible to decide what was the precise cause of death in these cases though autopsies were performed in all. In 4 peritonitis was a factor, possibly the major one; in 2 there was intestinal obstruction.

Both patients dying soon after operation had signs of circulatory collapse characterized by prolonged hypotension. Circulatory changes with hypotension were a marked feature of the clinical signs observed in most of the patients during this operation. Particular attention has been paid, therefore, to the circulatory changes in what follows.

The incidence of low blood pressure.—41 cases had hypotension of the order of 80 mm.Hg during the period of operation; 27 had hypotension in the post-operative period.

Since the anæsthetic may produce pressor effects on B.P. during its administration I have been careful to take account of the B.P. changes during the whole of the period of continuous observation which exceeds the period of operation in all but 2 cases.

The extent of the hypotension.—46 cases had systolic blood pressures of 90 mm.Hg or less. Thus practically all the cases had hypotension of this order at some time during the observations. In 9 the lowest level was between 80 and 85 mm.Hg. In 18, i.e. in over one-third, the lowest level was between 65 and 70 mm.Hg, in 5 the lowest level was 50–55 mm., in 1 it was 40 mm. and in 11 the B.P. was unrecordable.

The duration of hypotension.—Dr. Langton Hewer (1948) reports: "It has been said that a patient must not be left for more than 20 minutes with a systolic pressure below 80 mm.Hg or a diastolic pressure of less than 60 mm.Hg. If this time is appreciably exceeded death is extremely probable within 48 hours."

Hewer then adds that in his experience "patients can survive without apparent ill-effects for considerable periods with blood pressures so low that they cannot be measured".

Dr. Gillies (1948) has also noted that with total spinal anæsthesia in hypertensive patients the B.P. falls frequently to unrecordable levels, but gives no precise data relating to the duration of the hypotension. He wrote: "The clinical state described lasted an average time of 20 to 30 minutes, after which respiratory and circulatory function began to return to normal. Spontaneous pulmonary ventilation became adequate; the radial pulse again palpable, and the blood pressure although low, measurable."

Twenty-six of the patients (*see* Table V) having the synchronous combined operation had systolic pressures of 80 mm.Hg for periods of 20 minutes at least and yet 49 were alive four days after. It is therefore clear that this does not point to serious consequences in so far as life is concerned. In 30 cases the hypotension (80 mm.Hg) lasted for a period between 1–50 minutes. In this group the hypotension lasted between 1–20 minutes in 13 cases, and in 15 between 21–40 minutes.

The period during which the B.P. was unrecordable lasted only a short time. In 9 this did not exceed ten minutes. The longest period lasted 2½ hours, at the end of which time the patient died.

Blood loss at operation (*see Table II*).—15 had lost up to ½ pint (clinical estimate); 19 from 1 to 1½ pints. Only 4 lost 2 pints or over. Most of the loss came from the perineum. These losses represent external hæmorrhage and do not include extravasation of blood into the tissues.

Crook *et al.* (1946) have estimated blood loss during combined abdomino-perineal resections of the rectum in 12 cases, and found losses under 1 pint in 11 cases, of which 8 lost ½–1 pint. All had spinal anæsthesia.

Frankis Evans (1949) gives Dukes' figures as follows: "The average blood loss was between 500 and 1,000 ml. It was never less than 500 ml. and the highest figure he found to be 1,400 ml."

Normal man stands the loss of 1 pint of blood apparently without ill-effects other than an occasional fainting attack. Many normal men suffered injuries during the last war and lost as much as 2 pints of blood, and went through operation well some hours later. It does not follow that patients of the age group we are considering would tolerate relatively sudden losses of from 1 to 1½ pints under anæsthesia.

Transfusion of blood during operation (*see* Table II).—If the clinical estimates of blood loss are correct then most of the patients received blood in amounts equivalent to the losses or over (32 cases) by the end of operation. 6 patients did not have blood at all during operation though some of these had saline. Of the 20 patients whose transfusion of blood was less than the estimated loss the difference was more than 1 pint in only 5 of the cases.

TABLES II–V.—SYNCHRONOUS COMBINED OPERATION

Nos. in Body of Tables = Numbers of Cases

TABLE II.—BLOOD LOSS AND TRANSFUSION (BL & Tr)

	Clinical estimate of BL or Tr by the end of op'n (in pints)						Balance of Tr over BL by the end of operation			
	¼	¼–½	½–1	1–1½	1½–2	2	Under	Equal	Over	Not transf'd.
Transf'd. ..	4	3	17	13	5	4	20	18	14	6
BL.	6	9	9	19	5	4				

These findings suggest that low B.P. at operation is not due to loss of blood. We cannot be dogmatic because we do not know how much blood was extravasated. The next question is how much blood was lost by the time low B.P. (80 mm.Hg) was first recorded? Clinical estimates show that in the majority the loss did not exceed ¼ pint (34 cases) (*see* Table III). Since many of these patients had received some transfused blood by this time it is clear that loss of blood is not the initiating cause of the hypotension.

TABLE III.—CLINICAL ESTIMATE OF BL WHEN HYPOTENSION (80 mm.Hg) FIRST RECORDED

Pints BL.	?	Nil	VL	1/8	¼	½	⅝	1–1½	2	(VL—Hardly any)
Cases	1	18	10	1	5	4	1	2	1	

The circumstances attending the onset of low B.P. of the order of 80 *mm.Hg.*—Hypotension (of the order of 80 mm.Hg) was first recorded at three periods (*see* Table IV): (*a*) within the first 10 minutes (10 cases); (*b*) between 31 and 40 minutes (12 cases); and lastly (*c*) between 61 and 120 minutes (6 cases). Thus the periods were roughly early in operation, after half an hour and later.

TABLE IV.—ONSET OF HYPOTENSION (80 mm.Hg) AND OPERATION STAGE

Minutes:	0–10	11–20	21–30	31–40	41–50	51–60	61–90	91–120	121–150	151–180
Cases:	10	5	4	12	4	1	4	2	Onset of hypotension	
				Stages of Operation						
No. cases ..		18	28	5	1		having abdominal incision			
„ „ ..		1	30	18	2	1	„ peritoneum opened			
„ „ ..		2	18	22	8	2	„ perineum incised			
„ „ having bandages applied							16	22	9	3

These periods coincided with the steps of the operation. Most of the operations (22 cases) lasted between one and a half and two hours. 16 lasted between one and one and a half hours.

There is not a single instance of the incision of the abdomen before ten minutes. During this time the patients were given either a spinal or a general anæsthetic or both and then placed in the lithotomy-Trendelenburg position and catheterized. 5 of this group had a spinal anæsthetic and in 3 of these an intravenous barbiturate had also been given.

Hypotension occurring between 31 and 40 minutes corresponded to the time of the perineal incision in most of the cases. Immediately before the perineal incision was made the abdominal surgeon had explored the belly cavity to determine the operability or otherwise of the growth. At the time of the perineal incision the abdominal surgeon was usually stretching the attachments of the colon to the posterior abdominal wall.

Fig. 1 is a good example of a sudden fall in B.P. occurring at about this time in a patient who had lost less than ¼ pint of blood. Note how the systolic pressure was maintained at a steady level for the first 30 minutes although a spinal anæsthetic had been given. The 20 mg. methedrine which was given intramuscularly at one minute would presumably take about 15 minutes to act. It did not appear to have much effect unless it maintained the level for 30 minutes. The perineal incision was made at 28 minutes and 2 minutes later the surgeon was pulling hard on the rectum so that the patient's body shook. The colon was also being mobilized at the same time and hence it is not possible to decide which was the cause of the sudden fall in B.P. Had it been due to the spinal anæsthetic it would have begun to fall before. It might be argued that the pressor drug effect had worn off by this time so that the fall in pressure due to the spinal was delayed. As we shall see presently, however, a sudden fall at this period occurs with general anæsthesia without a spinal or a vasoconstrictor drug. Low B.P. due to nupercaine spinal anæsthesia does not occur suddenly half an hour after the intrathecal injection. I have already referred to cases with a fall in B.P. occurring within the first 10 minutes. One of these also had 20 mg. methedrine early on. Other similar results were also found with nupercaine in patients undergoing other types of rectal surgery. The clinical notes suggest the perineal manipulations were severe and it is possible that this region is the origin of an afferent depressor reflex.

The following events showed that the spinal anæsthetic was working: At 98 minutes the patient became conscious. Bandages were first applied by 109 minutes. At 128 minutes the perineal wound had to be exposed and reopened because of hæmorrhage. Hæmostasis was effected by 150 minutes. During these procedures the patient stated that he felt no pain although he was aware of the surgeon's manipulations.

Another point of interest is shown in Fig. 1. The abrupt fall in B.P. occurring at 90 minutes coincided with the change from the lithotomy-Trendelenburg to the dorsal position.

No large or moderate dose of kemithal was given at the times when the B.P. fell abruptly. The first fall occurred between 28 and 33 minutes. There were 3 doses of kemithal administered before this time, 0·6 gramme at 11 minutes; 0·3 gramme at 18 minutes and 0·2 gramme at 20 minutes. Practically no change in B.P. occurred for 8 minutes after the last dose. The second fall occurred between 88 and 93 minutes, the last dose of kemithal (0·1 gramme) being given at 76 minutes.

We can make the following deductions from this case:

(*a*) The spinal anæsthetic was effectively blocking pain sense.

(*b*) An abrupt and substantial fall in systolic B.P. occurred immediately after the perinea incision when the colon was being handled.

(*c*) The position remained constant.

(*d*) The perineal manipulations were sufficiently strong to cause jerky movements of the patient on the table.

(*e*) Neither the spinal nor the initial kemithal injections were followed by any significant lowering of systolic B.P. Subsequent doses of kemithal were less than the initial one.

(*f*) Blood loss was less than ¼ pint at the time when the B.P. had first fallen to 60 mm.Hg.

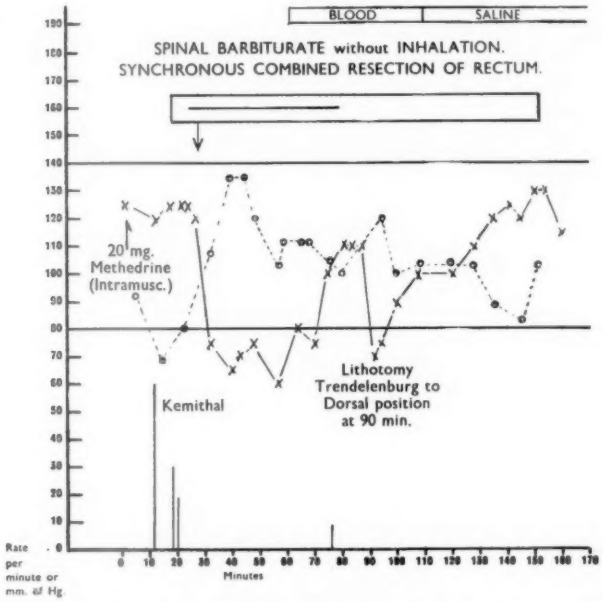


FIG. 1.—Blood loss: Very little by 47 min.; ¼ pint by 53 min.; 1 pint by 58 min. Transfusion by end of operation: Blood 1 pint; saline ¼ pint.

AN EXPLANATORY NOTE ON THE GRAPHS (FIGS. 1–5)

Crosses = Systolic B.P. Circles = Pulse rate/min.

Parallel lines at top of graph = transfusion.

Oblong = period of surgical manipulations; horizontal line within oblong = period of intraperitoneal manipulations; vertical arrow pointing downwards = perineal incision.

Vertical arrow with single barb pointing upwards = vasopressor drug.

Vertical lines at lowest part of the graphs = doses of barbiturate (10 = 0·1 gramme).

We have already stated that in a group of 12 cases hypotension of the order of 80 mm.Hg was first recorded between 31 and 40 minutes and that this period was the time when the perineal incision was made in 22 of the cases (Table IV). We shall see presently that abrupt falls in systolic pressure occurred in a significant number of cases at this stage of the operation even though it did not necessarily occur between 31 and 40 minutes.

Assuming this last statement to be correct then we can add that the evidence points to a perineal origin of a depressor reflex. In 2 cases the fall occurred after the skin incision but before the surgeon pulled on the rectum (one of these was a perineal resection of the rectum).

Overleaf is an example of a case in which the rectum is removed by the perineal approach some days after colostomy. This case has been chosen because of the clarity of the evidence and also because it shows the method of documentation.

NAME: C. C. No. B.4.

OPERATION: PERINEAL RESECTION OF THE RECTUM. Date: 27/7/48.
COLOSTOMY 10 DAYS PREVIOUSLY.

ANÆSTHESIA: SPINAL 2 c.c. 1 : 200 NUPERCAINE. NO GENERAL ANÆSTHESIA.

Mins. from zero	Time	Pulse	B.P.	Observations
−46	1540			Omnopon gr. ⅓, scopolamine gr. 1/150th subcutaneously.
− 4	1622	144	195/95	Sitting. Applying spirit to back.
− 2	24			Methedrine 30 mg. in ½ c.c. 1 : 200 nupercaine as local anæsthetic before lumbar puncture.
0	26			2 c.c. 1 : 200 nupercaine intrathecally between L. 2 and L. 3 spines.
2½	28½			Sitting position changed to dorsal.
5	31	148	205/110	
8	34			Sacral pad beneath buttocks and legs suspended in supports. Table is horizontal.
10	36		180/90	
14	40			Table wheeled into theatre and head end lowered 5 degrees.
16	42	152	190/100	Fingers warm; hand veins dilated, nose and forehead warm and dry.
18	44			Passing catheter.
21	47	152	195/90	Head end of table lowered from 10 to 15 degrees.
22	48			Towels arranged.
23	49	148	195/95	Suture of anus.
24	50			Incision of skin completely encircling the anus and growth which is plainly visible protruding externally. There are no facial grimaces and he says he does not feel any pain. Appreciates having his lips moistened.
27	53	144	185/90	The patient's head shakes with the perineal manipulations. A few oz. of blood loss now.
29	53	140	110/80	Radial pulse feels weaker but is regular. Fingers warm, forearm veins dilated. Nose and forehead warm. A very hot day. Dry skin.
32	58		80/	About 6 inches of rectum freed now. No more than ¼ pint of blood loss up to now. No transfusion.
34	1700	160	135/70	He says he is not in pain. Face colour not pale, it is slightly deeper than preop.
37	3	158	135/	No marked hæmorrhage. Now face is ? a little paler.
39	5	140	110/	Fingers, nose and forehead warm, dry skin. No change in face colour.
46	12	148	125/	No more than ¼ pint blood loss. No transfusion. Fingers warm. Has coughed about 3 times during operation. No sputum.
49	15	140	115/	Diathermy section of gut held in clamp. Face is a little paler than preop. but there is not much in it. There are only 4 fairly well-soaked dabs and there is not much more than ⅛ pint on the towels.

From this case we learn that:

(1) The spinal anæsthetic prevented the patient from feeling pain.

(2) An abrupt and substantial fall in systolic pressure coincided with perineal manipulations.

(3) The perineal manipulations were strong enough to cause slight jerky movements of the body.

(4) The systolic pressure was maintained for 27 minutes after the intrathecal injection.

(5) There were no abdominal manipulations.

(6) The position on the table was constant.

(7) Blood loss was minimal as determined by clinical estimate.

Surgical manipulations in the perineal region, which include skin and muscle incision and traction of the rectum, may produce a depressor effect on B.P. The afferent path for this reflex is not the path by which pain-producing impulses pass.

Fig. 2 shows a steady B.P. level during the first part of an abdomino-perineal resection of the rectum under general anæsthesia. The patient was then placed in the lithotomy position and the perineal part of the operation begun. An abrupt fall in systolic pressure coincided with the change of position and the perineal manipulations. No large doses of thiopentone were given at this stage, neither was there any sudden hæmorrhage. In the previous case (No. B.4) the change in position under spinal anæsthesia from dorsal to lithotomy did not

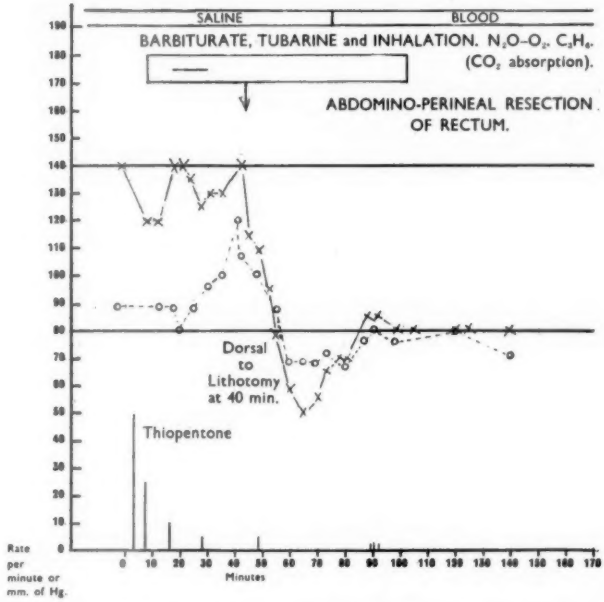


FIG. 2.—Blood loss: Very little by 49 min.; ½–1 pint by 55 min. Operative transfusion: Saline ½ pint; blood ½ pint.

produce a fall in B.P., whereas in Fig. 1 towards the end of operation a fall was associated with the change from the lithotomy-Trendelenburg to the dorsal position, there being no alteration with the initial position of the patient. I need further evidence on these points but at present suspect that the change from the dorsal to the lithotomy position is not associated with a fall in B.P. It has actually been advocated by Hingson and Southworth (1946) that a similar position to the lithotomy be used to treat cases with low B.P.

Although pressor factors at operation predominated in one group of cases, nevertheless some depressor response could be seen soon after the perineal incision. That the pressor factor was in some cases due to the anæsthetic was shown by the marked fall in B.P. on removing the mask of inhalation apparatus.

There were also examples showing a marked depressor effect coming on within the first ten minutes of the induction of analgesia. During this period the intrathecal injection of nupercaine, with or without an intravenous injection of barbiturate, had been made but the surgeon had not incised the skin. In some cases the fall occurred in spite of the previous use of vasoconstrictor drugs. When the perineum was incised later there was no change in B.P.

The abrupt fall in B.P. after the perineal manipulations have begun suggests, in the case of spinal anæsthesia, that the analgesic solution may not completely block the spinal pathways. It may be that only the nerve roots entering the spinal cord which are bathed in solution are blocked while the nerve fibres deep within the cord are free to transmit impulses. Thus if the roots in the lumbo-sacral region were not brought in contact with the anæsthetic, then impulses might enter here and pass up within the cord beyond that part which is in contact with the analgesic solution. One can readily imagine this happening with the Etherington Wilson technique.

Of the 32 synchronous combined abdomino-perineal operations performed with spinal anæsthesia, either alone or combined with general anæsthesia, no less than 12 had a steady level or a rise in B.P. before the perineal incision followed by a fall after it. This type of depressor response (not necessarily amounting to hypotension) was recorded in 1 out of 6 cases having spinal anæsthesia with 1 in 1,500 nupercaine by the Etherington Wilson technique; in 4 out of 6 with the Howard Jones technique and in 4 out of 6 with heavy nupercaine.

Early in the investigation I discussed the depressor responses occurring at the perineal stage of the operation with my colleagues in Leeds. As a result we decided to use what we then thought was a new technique. It consisted in giving heavy nupercaine to a patient in the sitting position and after 2 minutes injecting light nupercaine, keeping the patient sitting and continuing as in the Etherington Wilson technique. This method which we call the "combined" technique has been described before by Wilkinson (1942) who stated that it was first suggested to him by Nosworthy. We have been surprised to find a depressor response at the time of the perineal manipulations in cases conducted with spinal anæsthesia by Wilkinson's combined technique. It has been recorded in 3 out of 14 cases.

Further experiments have been tried. In 4 cases the perineum has been injected with procaine. One of these had a depressor response. In 4 the presacral region has been infiltrated with procaine. 3 of these cases had a depressor response at the time of the perineal manipulations. These experiments, which do no harm to the patient since they are normal procedures, involve small numbers of cases but are mentioned because I hope that others may be induced to use them to better advantage than I have been able to with the material in Leeds. They would be most usefully employed in the perineal resections of the rectum rather than with the synchronous combined operation, since we cannot be sure that the depressor responses occurring at the time of perineal trauma are not due to the abdominal manipulations.

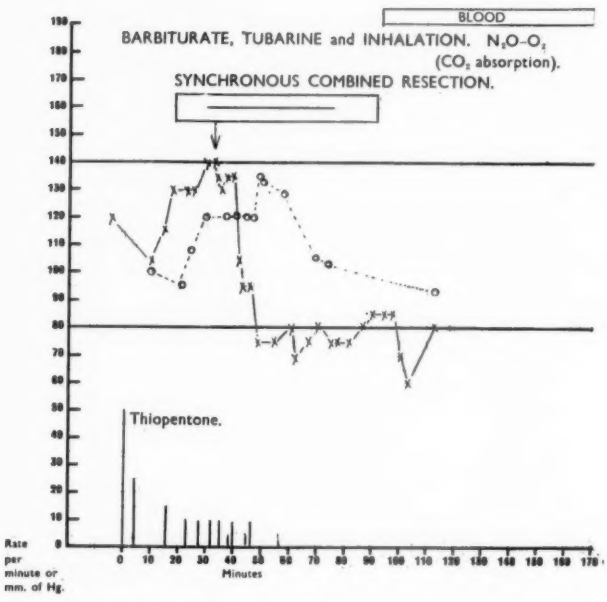


FIG. 3.—Blood loss: Very little by 27 min.; ½ pint by 42 min.; 1 pint by 59 min.; 1½ pints by 75 min. Transfusion: Nil during period of surgical manipulations.

Earlier, I mentioned an example of the depressor response occurring with general anæsthesia without spinal anæsthesia (*see* Fig. 3). In a group of 20 cases a depressor effect on B.P. was recorded in 11 cases beginning at the time of the perineal incision. I happen to have

a small series of upper abdominal operations conducted with the same method of anæsthesia. Out of 13 operations there was only one with hypotension. I rather suspect that pulling on the colon does not regularly produce hypotension.

The evidence which we have produced is that an abrupt fall in systolic B.P., during the synchronous combined operation, is related by time to the period when the perineal part of the operation is begun. This change has also been demonstrated in the perineal resection and also in the abdomino-perineal operation. Neither general nor spinal anæsthesia by various techniques, including the combined method, prevents the abrupt depressor change.

Another possibility is that the impulses which result from surgical trauma pass along nerves with relatively thick myelin sheaths. It is known that in the lumbar region there are many such fibres and that pain producing impulses pass along those with thin myelin sheaths.

It may be that the traumatic impulses pass to the spinal cord via the sympathetic or other nervous systems above the area which has been blocked by the spinal anæsthetic. Some of the sympathetic pathways pass into the upper thoracic segments of the cord. Hence the experiments with local infiltration in the presacral area.

Rovenstine *et al.* (1942) state that: "B.P. may change very little during high spinal anæsthesia in normal, unoperated man". Their interpretation of the significance of it is different from the one I have indicated above. They added: "The extreme falls observed in operated subjects are believed to be the result of decreased venous pressure (and hence decreased cardiac output) following opening the abdomen and the attendant operative procedures, inflicted in the face of vasomotor paralysis and loss of vasomotor defence."

We have already stated that there was a group of 7 cases developing hypotension of the order of 80 mm.Hg towards the end of operation. Besides these 21 showed a depressor response at the end of operation. In 6 cases this was considerable in extent (i.e. more than 70 mm.Hg). Scrutiny of the records shows that there were three circumstances occurring at this time: (1) the disconnexion of anæsthetic apparatus; (2) the reduction of the head-down table tilt; (3) the change from the lithotomy-Trendelenburg to the dorsal position. It was not possible in these cases to determine which was the major depressing factor as all three often occurred at about the same time. Fig. 4 shows a typical example.

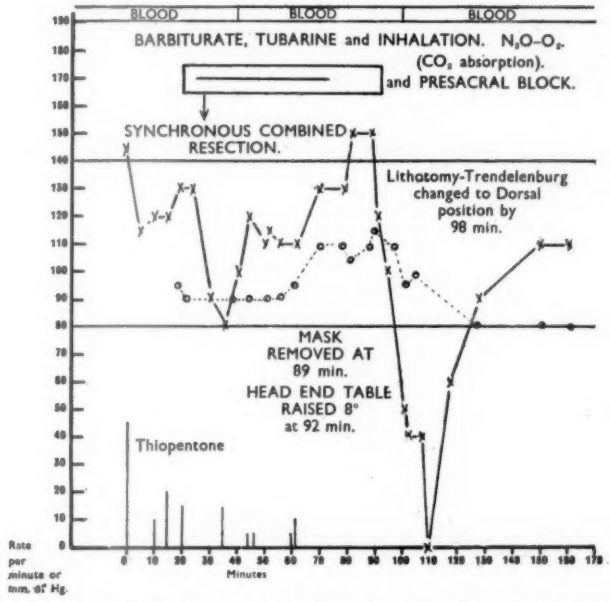


FIG. 4.—Blood loss: Very little by 27 min.; ¼ pint by 33 min.; ¾ pint by 53 min.; 1 pint by 71 min.; 1½ pints by 94 min. Transfusion: ½ pint blood pre-operatively, 1½ pints at operation.

Thus there are three periods of potential danger to the patient during the synchronous combined operation which are either at the beginning of anæsthesia, at the time of the perineal manipulations or at the end of operation. At such times deterioration shown by lowered B.P. may occur.

Attempts to control the blood pressure.—Vasopressor drugs were used in 26 cases, 19 had pholedrine, 4 ephedrine, 2 methedrine and 1 had icoral. In 5 the pressor drugs were given before operation but the remainder of these drugs were administered during operation.

Individual cases having pholedrine showed a rise of B.P. in practically all cases, the greatest being 115 mm.Hg. Hypertension resulted in 7 cases but was transitory. The pressor response was abrupt. In No. A.48 there was a rise of 65 mm.Hg in three minutes; in No. A.47 it was 75 mm.Hg in 6 minutes. The B.P. rise was not maintained as is well illustrated in Fig. 5.

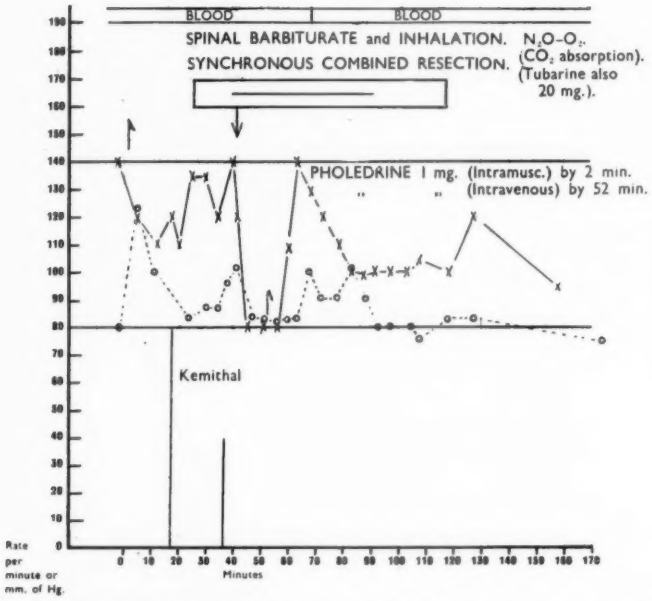


FIG. 5.—Blood loss: Very little by 44 min.; ¼ pint by 47 min.; ¾ pint by 101 min. Transfusion: ½ pint blood pre-operatively, ¾ pint at operation.

The whole effect appeared to be over in from 20 to 30 minutes after intravenous injection. The tendency of the B.P. curve appeared to be generally unaltered after the effects of the drugs had worn off.

After the intravenous injection of pholedrine it was possible to detect by ordinary palpation a narrowing of the radial pulse. This is direct evidence of peripheral arterial vasoconstriction. The superficial veins appeared to be the same width as before.

Vasoconstrictor drugs were used in only 2 of the cases with anæsthesia by inhalation and in 13 of the 21 with spinal and intravenous anæsthesia without inhalation. In both groups the incidence of hypotension of 80 mm.Hg maintained for 20 minutes was roughly the same. This suggests that these drugs were generally ineffective. In my opinion the best time to use them is at the end of operation if the B.P. falls as a result of the circumstances occurring at this time, which I have enumerated above. I have only used the continuous adrenaline drip (1 : 250,000) on one occasion in a patient with hypotension due to peritonitis some days after operation. Speeding the drip cautiously failed to have the desired effect. I am against the routine use of this method because its effects may conceal the true state of the patient, and it may constitute an unnecessary burden to the patient.

Comparisons of anæsthetic combinations.—Table V compares the effects of the main anæsthetic combinations. From these we note the following points some of which have been mentioned before:

(1) 5 cases having spinal and intravenous anæsthesia had losses of blood of the order of ¼ pint or less. None of the inhalation group had losses as small as this. The losses were on the whole greater in the inhalation group.

(2) Most of the cases were fairly well transfused by the end of operation. In many cases more transfusion was given after the end of operation.

(3) Vasopressor drugs were used mainly in the spinal group.

(4) Low B.P. of the order of 80 mm.Hg lasting for 20 minutes or more during the period of continuous observation occurred frequently and in approximately the same numbers in the two main groups.

(5) Rapid pulse-rates of the order of 120 beats per minute were found in about the same number in both main groups.

(6) Facial pallor was noted at operation in 15 of the main spinal group and in 7 in the inhalation group.

TABLES V, VI AND VII.—COMPARISON OF METHODS OF ANÆSTHESIA

TABLE V.—IN THE SYNCHRONOUS COMBINED OPERATION. (BL & Signs at Operation)

Total cases	Method of anæsthesia	Amounts BL (in pints) ¼	¼–½	½–1	1–1½	1½–2	2	Clinical signs Hypotension	Fast pulse	Pallor
20	Barb. and Inh. ..	—	1	4	10	3	2	11	7	8
21	Sp. Barb. No Inh.	5	5	2	7	1	1	9	6	15
4	Spinal „ „	—	3	1	—	—	—	2	1	3
7	Sp. Barb. and Inh.	1	—	2	2	1	1	4	5	7
52	Totals	6	9	9	19	5	4	26	19	33

TABLE VI.—AS FOR TABLE V BUT ALTERNATIVE PROCEDURES OF RESECTION OF THE RECTUM

1	Barb. and Inh. ..	—	—	1	—	—	—	—	—	1
1	Sp. Barb. No. Inh.	—	—	1	—	—	—	1	—	1
1	Spinal „ „	—	—	1	—	—	—	—	1	1
1	Sp. Barb. and Inh.	—	—	—	—	—	1	1	1	—
5	Ether Open ..	2	1	1	—	1	—	4	4	1
1	$CHCl_3$. Clover. ..	—	—	—	1	—	—	—	1	—
10	Totals	2	1	4	1	1	1	6	7	4

TABLE VII.—AS FOR TABLE V BUT INOPERABLE CASES: LAPAROTOMY OR COLOSTOMY

6	Barb. and Inh. ..	6	—	—	—	—	—	1	2	—
11	Sp. Barb. No Inh.	11	—	—	—	—	—	2	5	6
1	Spinal	1	—	—	—	—	—	1	—	—
2	Ether open ..	2	—	—	—	—	—	1	—	1
20	Totals	20	—	—	—	—	—	5	7	7

(NOTE.—Hypotension applies to the period of continuous observation. Other signs related to the period of operation. Fast pulse = 120 per minute, or more.)

It would appear that the inhalation group were in better shape at operation than the spinal and intravenous group if general condition went hand in hand with facial colour. The depth of facial colour soon decreased after the inhalation, and in some cases a marked fall in B.P. was recorded after the mask was removed. The amount of blood lost was more in the inhalation group. The 2 cases ending fatally within three hours of operation both had inhalation anæsthesia.

The patients with spinal and intravenous anæsthesia without inhalation looked paler at operation but this does not mean that they were in poorer condition; one of them vomited during operation. This is a distinct disadvantage but the anæsthesia produced by the barbiturates was no more than a sleep. It was not deep anæsthesia. On the whole I personally favour this method though I should prefer to give a stream of oxygen continuously via a small nasal catheter.

Findings During other Allied Surgical Procedures

The findings in cases belonging to the alternative operative procedures and in inoperable cases were as follows (*see* Tables VI and VII):

(1) Low B.P. and rapid pulse-rates were present in most of the small group of cases comprising abdomino-perineal, perineal resections and perineo-abdominal resections (Table VI).

(2) The last group (Table VII) shows the inoperable cases in whom nothing was done after the growth had been found to be too extensive for removal or in whom the liver was the seat of secondary growths. In a few of these a palliative colostomy was carried out. This group also includes one abdominal resection of the colon. Blood loss and transfusion was minimal in these cases. Hypotension of the 80 mm.Hg order lasting for twenty minutes or more was present in only 5 of the 20 cases.

Thus hypotension (80 mm.Hg for 20 minutes) occurred in ¼ of the cases having laparotomy and in ½ those with the synchronous combined operation. Blood loss was minimal in the former and was made up by transfusion in the latter group. Anæsthesia was roughly comparable; the main difference being in the amount of surgical manipulations. This may be the factor responsible for the difference in the extent of the hypotension, although as we have seen, hypotension was produced in the initial stages in some cases.

The Post-operative State (Synchronous Combined Operation)

I have indicated that the immediate post-operative period is a good time to assess the condition of the patient. I have classified the clinical signs in Tables VIII and IX.

Table VIII shows the states encountered in patients who did not have hypotension of the order of 80 mm.Hg in the post-operative period. The main point of importance is that practically all cases have a period when there are signs of vasoconstriction. Note also that the cooling of the extremities is not reflected by the temperature of the forehead. Changes in temperature were roughly assessed by the observers' warm hands.

Table VIII.—Synchronous Combined Operation. The Post-operative State in Patients without Hypotension of the Order of 80 Mm.Hg

No.	B.P. limits	P.R. limits	Face	Nose	F'hd.	Veins	Sweating	Restless (X)
			AFTER INTRAVENOUS BARBITURATE AND INHALATION ANÆSTHESIA					
A. 3	95–160	64–88	Pale	Cold	Warm		Nil	Nil
A.13	90–120	68–80	Pale	Cold	Cool	C	,,	Nil
A.18	105–140	60–88	Pale	Warm	Warm	C	,,	X
A.23	105–145	76–88	Pale	Cold	OffW	C	,,	Nil
A.24	90–110	76–88	Not pale	Cold	OffW	C	,,	Nil
A.26	90–115	72–76	Pale	Cold	Cool	C	,,	Nil
A.27	110–145	56–64	Pale	Cold	OffW		,,	Nil
A.41	85–105	104–120	Pale	Cold	OffW	N	,,	Nil
			AFTER SPINAL AND INTRAVENOUS BARBITURATE WITHOUT INHALATION					
A. 1	125–160	80–96	Pale	Cold	OffW		X	Nil
A. 4	90–180	100–128	,,	Cold	Warm		Nil	X
A. 8	105–110	60–68	,,	Cold	Warm		Nil	X
A.11								
A.12	88–165	88–104	,,	Cool	Warm		Nil	Nil
A.16	100	76	,,	Cold	OffW	C	Nil	Nil
A.34	100–185	48–80	,,	Cold	OffW	C	X	X
A.36	90–120	52–56	,,	Cold	Warm	C	Nil	Nil
A.38	85–125	72–100	,,	Cold	OffW	C	Nil	X
A.44	100–140	68–76	,,	Cold	OffW	C	Nil	Nil
A.50	95–115	76–80	,,	Cool	Warm	C	Nil	X
A.51	100–120	56–64	,,	Cold	OffW	C		X
			AFTER SPINAL ANALGESIA					
A.14								
			AFTER SPINAL AND INTRAVENOUS BARBITURATE AND INHALATION					
A. 6	85–105	80–88	Pale	Cold	Cool	C	Nil	Nil
A. 7	95–110	76	,,	,,	Warm		,,	X
A.25	85–125	80–88	,,	,,	OffW	C	,,	Nil
A.32	90–110	104–120	,,	,,	Warm		,,	Nil

C—constricted. N—normal.

Table IX shows the signs in those who had hypotension of the order of 80 mm.Hg in the post-operative period. I was unable to record the level of B.P. in 6 cases at varying times after operation. 2 of these died in the hypotensive state. In 12 cases B.P.s of 50 mm.Hg were recorded.

Pulse-rates of 120/minute or more were not frequent, only 7 cases having rates as fast as this in the whole series. Many cases in both groups had relatively normal pulse-rates.

The point to note about these two Tables is that vasoconstriction was a state common to both groups and that the distinguishing feature was the level of systolic blood pressure. The state of vasoconstriction does not *per se* mean that the patient is ill.

Since periods with systolic pressures in the region of 80 mm.Hg occur in roughly half the cases this state, even with vasoconstriction, does not indicate that serious consequences will follow from a circulatory point of view. The 2 patients who died soon after operation had either pressures about the 40 mm.Hg level or the pressures were so low as to be unrecordable. These low pressures were accompanied by fast pulse rates. Pulse-rates varied in those who recovered with low B.P., but they were mainly below 100/min.

These findings indicate that systolic levels about 50 mm.Hg are to be regarded as definite signs of circulatory danger during the post-operative period.

TABLE IX

No.	B.P. limits before level reached 100 mm.Hg	Minutes from bandages to time when B.P. reached 100 mm.Hg	Clinical signs when B.P. below 100 mm.Hg: Pulse-rate limits	Face colour	Temp. of Nose	Temp. of Forehead	Veins	Sw.	Restless
			AFTER INTRAVENOUS BARBITURATE AND INHALATION ANÆSTHESIA						
A.5	*UR–40*	D.162	120	Pale	Cold	Off warm	C	Nil	Nil
A.17	60–80	103	90–92	,,	Cool	Off warm	C	,,	,,
A.19	50–90	282	80–96	,,	Cool	Cool	C	,,	,,
A.20	70–90	67	56–100	,,	Warm	Warm	C	,,	,,
A.21	75–85	99	80–112	,,	Cold	Warm		,,	,,
A.30	75–95	404	96–108	,,	Cold	Cool		,,	,,
A.33	*UR–90*	59	80–108	,,	Cool	Warm	C	,,	,,
A.35	80	12	68						
A.40	*UR–55*	D.154	Rapid	,,	Cold	Warm	C	,,	,,
A.42	60–90	45	56–60	,,	Warm	Off warm		,,	,,
A.43	60–90	33	48–76	,,	Cool	Off warm	C	,,	,,
A.45	*50–75*	114	52–80	,,	Cool	Off warm	C	,,	,,
			AFTER SPINAL AND INTRAVENOUS BARBITURATE WITHOUT INHALATION						
A. 2	*40–95*	240	104–120	Pale	Cool	Warm	C	Nil	+
A.22	70–95	?	48–60	,,	Cold	Warm	C	Nil	+
A.29	*UR–80*	35	48	,,					
A.37	80–92	10	52–60	,,	Cold	Off warm	C	Nil	Nil
A.46	55–95	?	60–84	,,	Cold	Off warm	C	Nil	Nil
A.48	75–90	481	72–84	,,	Cool	Cool	C	+	+
A.49	*50–75*	276	56–92	,,	Cold	Off warm	C	+	Nil
A.31	75–115	127	72–82	,,	Cold	Warm	C	Nil	Nil
			AFTER SPINAL ANALGESIA ALONE						
A. 9	50–80	40	80	Pale	Cool	Off warm		Nil	Nil
A.39	60–90	480	44–68	,,	Cold	Off warm		Nil	Nil
A.47	*UR–90*	?	56–64	,,	Cool	Cool	C	+	+
			AFTER SPINAL AND INTRAVENOUS BARBITURATE AND INHALATION						
A.10	60–80	?	84–120	Pale	Cool	Cool	C	+	+
A.15	55–90	44	96	,,	Warm	Cool		+	Nil
A.28	*UR–85*	265	76–104	,,	Cool	Cool	C	Nil	+
A.52	*45–90*	345+	64–112	,,	Cold	Off warm	C	+	+

Degree of hypotension and post-operative state in patients after the synchronous combined operation. (Only includes those with pressures of 80 mm. or less.) D – died soon after operation.

The R.R.H. CO_2 Indicator

I have previously referred to pressor changes at operation which may be due to the inhalation of an excessive amount of CO_2 gas in rebreathed mixtures.

Dr. S. T. Rowling, Mr. Ringrose and myself (1950) have together produced an instrument which is capable of measuring CO_2 reasonably accurately in the presence of other anæsthetic gases. It can be used continuously during the administration of anæsthesia and is being used by us now to investigate the pressor changes due to anæsthesia. A detailed account of the instrument will be found in the *British Journal of Anæsthesia*.

Summary

The need for the application of Clinical Science to anæsthetic problems has been stressed. The disadvantages of the present system of recording in anæsthesia have been exposed and an example of a more adequate documentation illustrated. The material offered by clinical hospital practice did not lend itself to research as in the laboratory, yet the *method of observation*, as illustrated in this paper, was confined to specific groups of operations in man and, further, comparisons of the effects observed enabled what was tantamount to the *method of experimentation*, without subjecting the patient to any unnecessary procedure.

Hypotension was a characteristic feature of the *synchronous combined* abdomino-perineal resection operation and, in spite of this, the majority of patients recovered. 2 of the 52 cases died soon after operation with prolonged hypotension (40 mm.Hg and unrecordable). The observations indicated that external blood loss is not the cause of hypotension.

Three periods of deterioration as shown by a fall in B.P. occurred either initially—between 31 and 40 minutes from the beginning—and at about the end of operation. The factor operating initially was mainly the anæsthetic; between 31 and 40 minutes, the perineal and abdominal manipulations; at the end of operation the three factors were: (*a*) levelling of the table, (*b*) change from the lithotomy-Trendelenburg to the dorsal position, and (*c*) release of anæsthetic pressor influences.

Records made of the clinical signs in the *perineal* and the *abdomino-perineal* resections of the rectal operations, pointed to a depressor effect on B.P. at the perineal stage irrespective of changes in position.

Modifications in the technique of spinal anæsthesia failed to prevent depressor effects on B.P. at the perineal stage of the *synchronous combined* abdomino-perineal operation.

Surgical manipulations in the perineum (without abdominal manipulations) under spinal analgesia alone, resulted in a fall in B.P. although no pain was experienced by the patient.

The use of vasopressor drugs (mainly pholedrine) did not materially alter the general B.P. curve at operation. A comparison of anæsthetic combinations with the *synchronous combined* operation indicated that blood loss was less in the group having spinal and I.V. barbiturate without inhalation, compared with the group having I.V. and inhalation anæsthesia, with a muscle relaxant drug. Facial pallor occurred in twice as many cases in the spinal as in the inhalation group.

A study of the post-operative stage shows that vasoconstriction, particularly of the face and limbs, was common to most of the cases and indicates that the critical level of B.P. is about 45–50 mm. of Hg.

My thanks are due to all those who have assisted me in this work and, in particular, to the anæsthetists and surgeons of the Leeds United Hospital.

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Section of Dermatology

President—W. N. GOLDSMITH, M.D., F.R.C.P.

[*December* 15, 1949]

Case for Diagnosis. ? Dermatitis Nodularis Necrotica.—R. E. CHURCH, M.B., for C. H. WHITTLE, F.R.C.P.

D. B., male, aged 33. Two years' history of an itching eruption on the trunk, limbs, neck and face; the lesions commence as papules, become pustular and ultimately ulcerate leaving scars. Hæmorrhagic lesions have been noticed on the hands. Relapses occur in crops with mild fever; the last severe crop was four months ago. A few active lesions are always present.

Admitted one year ago to Addenbrooke's Hospital, Cambridge, after a hæmatemesis of 2 pints, subsequently shown by barium meal to have been caused by a subacute duodenal ulcer. A test meal, however, showed complete achlorhydria. Ulceration of the palate and fauces was then present which has left similar scars to those on the skin.

In 1943 he had malaria and dysentery while in Egypt.

On examination.—The patient is puny and sallow-complexioned. Multiple varioliform scars, some pale, others pigmented, are present over the face, lips, palate, neck, limbs and trunk.

Active lesions in all stages, from red papules and papulo-pustules to indurated nodules with an ulcerated centre, are present over the dorsæ of hands, the arms and trunk (Fig. 1). The ulcers are circinate, deep and about 1 cm. in diameter, forming ultimately a dry scab, then healing (Fig. 2).



FIG. 1.—Distribution of eruption.

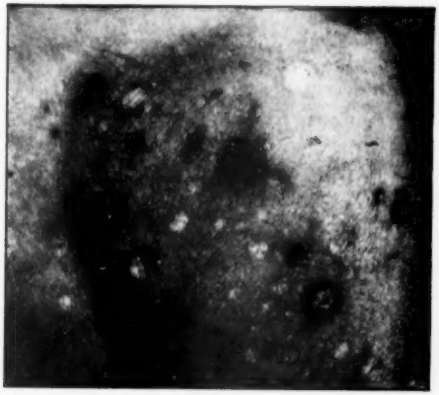


FIG. 2.—Showing necrosis and scars over shoulder.

(Photographs by Mr. K. Titterington.)

There is a generalized lymphadenopathy consisting of firm, discrete, painless glands. The liver and spleen are impalpable.

No abnormality detected in other systems.

Investigations.—Mantoux test negative (including 1 : 10). X-ray chest, lungs clear. W.R. and Kahn negative. Blood count, an eosinophilia of 21% of 8,100 white cells.

Sternal puncture normal, save for slight eosinophilia.

Sedimentation rate (Westergren) 26 mm. (= 12 mm. corrected) per hour.

Biopsy of an early papule shows a wedge-shaped area of necrosis involving the epidermis and superficial corium surrounded by a cellular infiltrate which tends to be perivascular and consists of histiocytes and lymphocytes with very few other cells. The vessels in the papillary layer are dilated, with a surrounding cellular infiltrate throughout the length of the section.

Biopsy of a cervical lymph gland shows only inflammatory change with much hæmosiderin present.

Comment.—The nature and course of the lesions together with the absence of signs of tuberculous infection suggest the diagnosis of dermatitis nodularis necrotica, in which disease the hypothesis of a tuberculous ætiology has been discarded (Sutton and Sutton, 1949). Three recorded cases of this disease have had similar necrotic ulcers in the mouth (Duemling, 1936; Cannon, 1930; Niemann and Wise, 1939).

The histological structure, which shows inflammatory change in and about the blood vessels with a secondary necrosis, has suggested an embolic process (Duemling, 1930; Jablonska, 1949), but in most reported cases attempts to isolate the causative organism or find a focus of sepsis failed.

In this patient the white blood cell count shows a marked and constant eosinophilia which may indicate an allergic rather than an infective process.

POSTSCRIPT (12.5.50).—The patient has recently developed an acute gangrene of the right index finger. There is now an eosinophilia of 32% of a total W.B.C. count of 17,000, many of the eosinophils being vacuolated—(Dr. Martin Hynes).

Although no further confirmation can be obtained, it seems possible that this may prove to be a case of periarteritis nodosa.—R. E. C.

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Dr. H. Haber: I have seen a case in a woman of 30 who for the last fifteen years has been suffering from ulcers of the mouth and vulva. She also had acneiform pustules of the face. The ulcers in the mouth were of the aphthous type and left deep scars. The ulcers on the vulva closely simulated those seen in Dr. Whittle's case. They, too, left scars. Biopsy performed on an ulcer of the vulva disclosed a peculiar histological picture similar to that seen in reticulosis. There were no changes indicating periarteritis nodosa. I feel that we are dealing here with a virus infection.

? Reticulosarcoma. ? Eosinophilic Granuloma.—C. H. WHITTLE, F.R.C.P., A. LYELL, M.B., and R. E. CHURCH, M.B. (Shown by permission of Professor J. S. MITCHELL and Dr. M. BENNETT).

K. R., a farmer, aged 45.

Presenting symptoms were enlarged lymph nodes at back of neck noticed two years ago. Others appeared in epitrochlear and inguinal groups. There was also a rash in the groin. The left upper eyelid showed infiltration one year ago and in the last three months there appeared the swellings now present on the face, and his general condition has deteriorated.

He also has considerable œdema of feet and legs, and subcutaneous lumps on the dorsa of hands. ? "ganglia". On the trunk and legs there is some marmorate erythema, but no tumours are present. The liver and spleen are grossly enlarged and so are axillary, epitrochlear and inguinal lymph nodes. There has been no generalized pruritus.

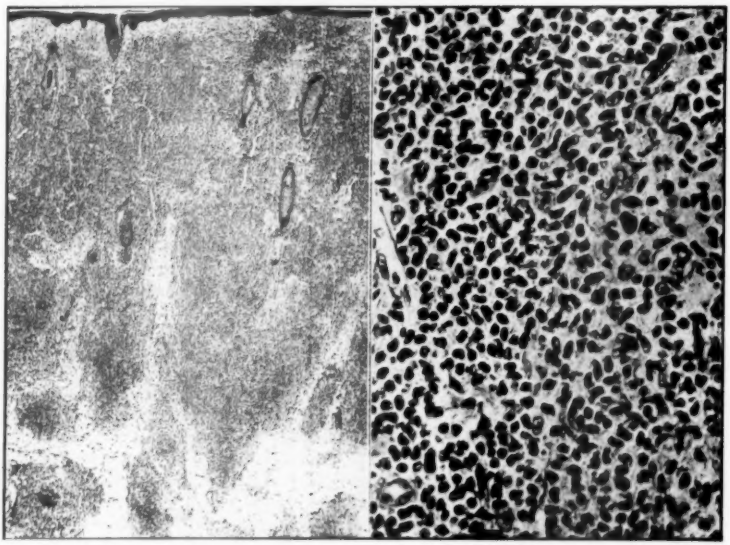


FIG. 1. FIG. 2.

FIG. 1.—Low power. Showing the thickness of skin and subcutaneous tissue involved.

FIG. 2.—High power. Showing primitive cells with abundant cytoplasm and reticulum fibres. (Photographs by S. W. Patman.)

The facial lesions, which are reminiscent of leukæmia, are striking and consist of bluish-red induration and infiltration of the skin and subcutaneous tissues, with gross enlargement of the forehead, nose and cheeks and upper eyelids. There has been constant eosinophilia in the blood, which has varied from 40–45% (5,000 to 11,000 per c.mm.).

W. and Kahn negative. Nasal swabs: Hansen's bacillus negative.

Blood count (9.12.49, Dr. J. Marx).—Red cells 4,230,000; Hb 11·4 mg. per 100 ml.; Leucos. 12,000 (neutros. 40·5, eosinos. 45, basos. 0·5, lymphos. 11, monos. 3% per c.mm.)

Sternal marrow count.—Eosinophilia only; no other abnormality. Eosinophil myelos. 5·8%, eosinos. 11·6% (Dr. F. W. Gunz).

Chest X-ray: Enlarged right hilar gland. Effusion right base (Dr. ff Roberts).

X-ray of long bones revealed no abnormality.

Biopsy of first and second lymph glands (cervical) (28.7.48 and 27.4.49).—Eosinophils present in the connective tissue outside, very few in the pulp. Probably reticulosis; no evidence of Hodgkin's disease. *Biopsy of third lymph gland* (2.12.49).—Vascular changes are the most striking feature. The arterioles of many of the follicles are converted into whorls of fibroblast-like cells, and in many of the (larger) arterioles in the capsule of the node there is intimal thickening, often with reduplication or interruption of the internal elastic lamina. One arteriole has fibrin and red cells in a segment of its wall. There is no cellular infiltration in or around the affected vessels. *Biopsy of eyelid* (28.7.48).—Much cellular infiltration; the predominant cells appear to be lymphocytes, but there are abundant eosinophil leucocytes and apparently frequent plasma cells; not suggestive of Hodgkin's disease; probably a reticulosis (Dr. A. M. Barrett).

Skin biopsy (taken 7.12.49: report received 15.12.49).—There is massive cellular infiltration deep in the corium, but reaching right up to the epidermis (*see* Fig. 1). The cells vary

considerably in appearance, but are not divisible into distinct types. The smaller cells resemble large lymphocytes but there are also frequently larger cells which do not correspond with any normal forms (*see* Fig. 2). It is amongst these that mitoses are fairly frequent. There is an abundance of reticulum fibres probably intimately related to the cells. There are occasional eosinophils but these constitute only a very small proportion of the free cells. There are small foci of fibrinoid degeneration. Vascular changes present are similar to those described in the lymph node.

The picture does not suggest Hodgkin's disease or mycosis fungoides, and on the whole fits in more with reticulosis or reticulo-sarcoma, with the balance slightly in favour of the latter: on the other hand the vascular changes and the blood eosinophilia suggest an allergic state (Dr. A. M. Barrett).

Dr. Whittle: The skin biopsy report, received only to-day, showed that this condition, in spite of the persistent high blood eosinophilia, is not in fact an eosinophilic granuloma. Moreover the process, whatever it be, is affecting other organs besides the skin. Weidman (1947) and Lewis and Cormia (1947) have thrown doubt on the existence of the eosinophilic granulomas of the skin.

Four days ago the patient had X-ray treatment to his right forehead, and I think the lesion on the right forehead is smaller than on the left, and that it is responding. If this patient is to be irradiated, he must be irradiated all over; it may be, however, that nitrogen mustard may prove a more effective therapeutic measure.

I recall a remark by the President on the reticuloses (1944): "We clinicians must not throw up the sponge and just let it drop anywhere in the reticular basket; it will remain our job to differentiate, for that is the meaning of diagnosis."

POSTSCRIPT.—1.2.50: The lesions on the face have almost disappeared following the X-ray treatment, but X-ray treatment to the trunk has not been followed by lessening of œdema in arms and legs.

28.2.50: After X-ray treatment—500 r to face, neck, axillæ and groins—the lesions have practically disappeared leaving only patches of erythema on the face. The œdema of the arms and legs has almost disappeared and his general condition has gradually improved. The tumours appear therefore to be highly radio-sensitive (C. H. W.).

20.5.50: The response to irradiation was unusual in that it was slow, but up to date the condition has cleared completely, and has shown no tendency to recur, and the patient is up and about (Dr. M. Bennett).

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Eosinophilic Granuloma of the Skin.—A. J. ROOK, M.B.

A married woman, aged 68. In April 1949 she noticed a small brown spot on the nose, which has slowly enlarged.

She is the mother of 3 healthy children now aged 34, 33 and 28, and until 1945 had never been seriously ill. In January 1946 she was referred to a Chest Clinic on account of a cough which had become worse over a period of three to four months. Dr. J. H. Dadds reports: "When she was first seen at the clinic her chest X-ray showed exudative infiltration in the right upper lobe. Sputum was positive for tubercle bacilli on more than one occasion. She made very good progress with prolonged bed-rest followed by sanatorium course, with fibrosis and healing of the lesions which have been regarded as quiescent since early in 1947." Her general health is now excellent.

Examination.—On the right side of the nose is an infiltrated slightly raised, sharply defined plaque about 1 cm. in diameter, brownish-red in colour and rubbery in consistency.

General physical examination reveals no abnormality other than diminished air entry and some dullness to percussion in the right upper chest.

Blood count (20.11.49).—Total white cells 6,300 (polys. 39, eosinos. 3, lymphos. 55, monos. 3%).

Blood Wassermann ++, Kahn, strong positive.

Biopsy.—The very small specimen obtained shows the dermis to be heavily infiltrated by lymphocytes, plasma cells and a large number of eosinophils.

Comment.—The resemblance of this case both clinically and histologically to those shown to this Section by Wigley (1945) and Borrie (1949) is remarkably close. The literature on eosinophilic

granuloma of the skin is very confused, as the term has not been restricted to any single clinical or pathological entity. Lever, *et al.* (1948) pointed out that among the heterogeneous collection of cases recorded under this diagnosis, there is a group of cases showing a number of features in common. The patients are characteristically middle-aged men or women, who develop on the face from one to five purplish or reddish-brown infiltrated plaques from 1 to 10 cm. in diameter. The lesions persist indefinitely and are not permanently influenced by fractional X-ray therapy. There is no evidence of involvement of any other system. Histologically the lesions show a mixed dermal infiltrate in which eosinophils are present in large numbers.

This case and Wigley's and Borrie's cases are all apparently identical with those collected by Lever. The positive blood W.R. is interesting, and the patient will be given specific treatment, but it seems improbable that the skin lesion is related to the syphilitic infection.

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Dr. H. J. Wallace: These cases seem to afford a good example of the differentiation Dr. Rook mentioned between this so-called eosinophilic granuloma with a characteristic clinical and histological appearance, and other granulomata of varying appearance both clinically and histologically, with eosinophilia as an incidental finding. The characteristic appearance of the first type seems to be a localized infiltration of the skin with this curious bronze colouring. Dr. Whittle has mentioned the number of reticulocytes and eosinophils which are to be seen in his case, but there is no reason to suppose that this is related to the eosinophilic granuloma shown by Dr. Rook. For example, some patients who show the clinical course of mycosis fungoides may have lesions apparently granulomatous in character with a predominance of eosinophilic cells.

? Lichen Nitidus.—A. D. PORTER, M.D.

Woman, aged 60.

History of nasal catarrh, pneumonia and pleurisy (no fluid).

An eruption on the trunk was first noticed two years ago and since then has spread slowly to limbs, neck and face.

Examination showed numerous discrete papules 1–3 mm. in width, scattered over the trunk and limbs, with many pigmented macules. The papules are pink, yellowish, or flesh-coloured, and some are flat-topped and lichenoid, while others are dome-shaped and covered with a scale attached at its periphery and free in the centre. Some of the papules resemble "apple jelly" when seen through a glass slide under pressure and suggest a tuberculide. Fading papules tend to be replaced by a pigmented macule.

Biopsy showed a typical tuberculous structure. No acid-fast bacilli were seen and guinea-pig inoculation was negative.

Skiagrams.—Chest, thickened pleura at the right base; sinuses, thickened lining of the right antrum; bones of the hand showed no abnormality.

Mantoux, 1:10,000, was negative on two occasions.

Blood showed a mild secondary anæmia.

Sarcoidosis may be excluded.

It occurred to me that the case rather resembled one shown by Dr. Wallace about a year ago as lichen nitidus.

Dr. H. Haber: The histology revealed a tuberculoid granuloma arranged round blood vessels and situated within the upper third of the corium. It resembled lupus vulgaris or tuberculoid leprosy. There was a rather increased lymphocytic infiltration round foci of endothelial cells, pointing against a diagnosis of sarcoid. I think this case belongs to the group of papular tuberculide.

Erythema Induratum (Whitfield).—F. RAY BETTLEY, F.R.C.P.

D. C., unmarried, aged 50. Manageress. Occupation involves standing all day.

History.—Ovarian cyst removed thirty years ago. Rheumatism in knees and elbows. Has had varicose veins for twelve years. Had a right Trendelenburg operation in 1948.

Family history.—Two brothers died of pulmonary tuberculosis. One sister died of cancer. One brother and two sisters alive and well.

Present illness.—For ten years tender red nodules have appeared on the calves, anterior surfaces of thighs, on the buttocks, arms and forearms. In size they are up to 1 in. in diameter. Their colour gradually changes to purple and after some months they disappear, leaving a pigmented stain. None of the lesions has ever ulcerated or discharged. There appears to be no clear seasonal variation.

On examination.—Several slightly tender nodules are to be felt, varying in size from ¼ to ½ in. in diameter. Many of them have left a residual brownish pigmentation. The lesions are chiefly to be found on the calves, with isolated ones on the other parts mentioned. A few inches above the ankle several lesions have run together to form a purple indurated area 2 or 3 in. across. The legs feel rather cold, but vascular pulsation is within normal limits.

General examination revealed no abnormality. B.P. 140/90.

Blood.—W.R. negative; normal blood count; blood urea normal; serum protein 7–8 grammes %; A/G ratio 1·2/1.

Skiagrams of chest, hands and feet, soft tissues of legs were all normal. Mantoux 1 : 1,000 negative, 1 : 100 strongly positive.

Biopsy (lesion about 2 weeks old, from the leg).—Histological section shows the main changes to be situated in the hypoderm. The epidermis shows a little hyperkeratosis, and in the dermis there is some perivascular round-cell infiltration.

In the fatty tissue of the hypoderm is a necrotic area, and much of the surrounding tissue shows cellular infiltration. This dense infiltration contains, in places, a fair number of polynuclear cells, but is, for the most part, made up of histiocytes and fibrocytes. One or two giant cells of the foreign body type can be found, but they are not a prominent feature. Two surprisingly thick vessels are present in the section. They are not degenerated, inflamed or thrombosed and appear to show either simple hypertrophy, or are rather large arterioles strongly contracted down. Serial sections do not show vascular thrombosis.

Comment.—This non-tuberculous form of erythema nodosum appears to have been first identified by Whitfield (1901) and subsequently mentioned by him in 1905 and 1909. He points out that erythema induratum in women under the age of 25 is nearly always tuberculous, and that over 30 it is nearly always not.

A case of apparently similar sort was shown here by Forman in 1938 under the name of lipophagous granuloma, a name coined, I believe, by Telford (1937) to describe lesions of this kind. Included under this heading are the similar lesions on the legs seen in old poliomyelitis patients. In the discussion at that time Sir Archibald Gray said that Dr. Forman's case was in the same class as Whitfield's erythema induratum.

The present case appears to fit in closely with Whitfield's description and also with the condition described by recent American authors as nodular vasculitis.

Montgomery *et al.* (1945) mention all the features of to-day's case and finally they say that they do not know what the condition is. It seems a pity to resurrect this morbid entity under a new name and to discard the name of Whitfield who originally described it.

Although there are conspicuous vascular changes they appear to me to be hypertrophic or obliterative rather than inflammatory. For this reason the term vasculitis may not be a happy one, but it seems that Telford was right in saying that the changes in the fatty tissue are vascular in origin.

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Dr. Arthur Rook: In France cases of this type and Bazin's disease are grouped together under the convenient but purely morphological designation of "dermohypodermites nodulaires" and are considered to be "allergides". Whereas Bazin's disease is accepted as being of tuberculous origin, these other cases are regarded as a similar type of reaction to the streptococcus and are said sometimes to respond to treatment with sulphonamides.

Dr. P. J. Feeny: I have had one example of this condition in which the patient also had scrofuloderma in an abdominal scar and phlyctenular conjunctivitis.

Mycosis Fungoides.—P. HUGHES, M.R.C.P. (Introduced by J. E. M. WIGLEY, F.R.C.P.).

Past history.—W. T. B., aged 68. A Commercial Traveller in paraffin oil. Enjoyed good health from the age of 15 until six years ago.

At the age of 15 shortly after commencing handling paraffin oil he suffered from a red scaly type of rash, which apparently cleared up in a few weeks.

He was very worried in 1944 following loss of shop by fire, and received medical attention for some weeks because of insomnia, nervousness, &c.

Family history.—One sister had eczema when infant. Nothing else of importance.

Present illness.—June 1948 first noticed red, scaly patches on front of legs, extending from just below the knees to one inch above ankles. Severe itching in these areas prevented

the patient from concentrating on his work. Troubled by lack of sleep on account of persistent pruritus. He sought advice after a month from Medical Practitioner.

June 1948–January 1949 he was treated by sedatives, and local application of calamine lotion.

The eruption had gradually spread to trunk, limbs, scalp and face so that when I first saw him on January 18, 1949, in the Out-Patient Department he appeared to be suffering from severe exfoliative dermatitis and complained of intractable pruritus.

General physical and special examinations.—The patient was well-developed slightly obese man of medium stature. His B.P. was 220/110. Heart sounds of good quality. Aortic second accentuated. Lungs—B.S. clear. Abdomen, liver and spleen not palpable.

The skin was red and somewhat indurated, and was shedding large sheets of thick scales.

Pupils: Equal reacting to L and A.

Discs: No papillœdema. Retinal arteries tortuous.

C.N.S.: N.A.D.

E.C.G.: Left axis deviation plus evidence of left ventricular strain.

X-ray of chest shows enlarged heart. Hypertensive type.

X-ray of both hands and feet normal.

Laboratory data: Urine normal on several examinations. Blood urea 30 mg. per 100 c.c.

Blood counts.—10.2.49: R.B.C. 5,270,000; Hb 100%; C.I. 0·96; W.B.C. 9,600. Differential: Neutros. 64%, eosinos. 1%, monos. 3%, lymphos. 32%.

7.12.49: R.B.C. 5,200,000; Hb 85%; C.I. 0·81; leucocytes 5,200. Differential: Neutros. 70%, monos. 4%, lymphos. 26%.

Treatment.—Rest, sedation for pruritus. Antihistamine drugs and local applications—calamine and hydrarg. perchlor. 1:10,000. Vitamins A.B.C.D., &c.

He was discharged from hospital on 14.2.49 very much improved.

As the pruritus often worried him at night and the skin retained its red hue with areas of small scaly patches on the trunk the patient continued to attend O.P.D. for observation.

In May a nodule appeared on the back of left hand—excision (Histological report—Epithelioma).

Later subcutaneous nodules were noticed on back of both hands and forearms. These have gradually increased in size and are now about the size of marbles.

Biopsy of a nodule (Histological report *see below*).

In June the pruritus again flared up. The patient was kept on vitamins, antihistamine, and in addition was given a course of B.A.L. An improvement was noticed in the skin which now no longer sheds, and the pruritus has disappeared. The redness and induration have, however, remained.

Short review of literature.—The exact nosological position of mycosis fungoides is still far from settled. The non-characteristic clinical and histological picture of the early premycotic phase lasting for weeks or years does not help in diagnosis.

Besnier [1]: "A chronic ambiguous pruritic dermatitis rebellious to ordinary treatment, and which assumes the form of a vague erythrodermia, &c. It is always necessary to bear in mind the question of a possible mycosis fungoides."

Ewing [2] stated that "mycosis fungoides is a reticulum cell lymphosarcoma originating from reticulo-endothelial cells".

Frazer [3] believed that "inflammatory reactions observed during the premycotic stage are due to the developments of tumour cells".

Montgomery [4] states that the histopathological changes in the early premycotic stage are inflammatory, and only later on that transition to lymphoblastoma becomes apparent.

Hynes [5] reported "An associated squamous cell carcinoma of face"—in his case of mycosis fungoides.

Histological report (Dr. C. N. Partington).—Section shows an inflammation of the skin. There is an acanthosis involving chiefly the interpapillary processes which have become lengthened. The stratum granulosum is not well defined and in places absent and the cells replaced by parakeratotic horn cells. The papillar and subpapillary vessels are dilated and surrounded by zones of lymphoid cells. The leucocytes have in places found their way to places between the prickle cells and some are collected superficially. The appearances are consistent with psoriasis. There is no evidence of Hodgkin's, or leukæmic infiltration. The appearance is not that of a *typical* mycosis fungoides.

In view of the history and the findings I think it advisable for me to send the slide with notes to Dr. W. Freudenthal, Reader in Dermatological Histology, University of London.

Histological report (Dr. W. Freudenthal).—The histological diagnosis rests between psoriasis and the pseudo-psoriatic picture that is frequently produced in mycosis fungoides (or rather premycosis) when the infiltrate in the uppermost layer of the cutis presses

against the epidermis and elongates the papillæ. I would prefer the latter diagnosis: the infiltrate is somewhat denser and more numerous than usually found in psoriasis, it also reaches deeper down and does not always seem to be connected with the epidermal changes. Generally, one gets rather the impression of a cutaneous process producing secondary epidermal changes than of a true epidermo-dermal process, as in psoriasis. Though the biopsy, in my view, is in accordance with and supporting the clinical diagnosis of mycosis fungoides (or an allied reticulosis), you were fully justified in raising the question of psoriasis as a differential diagnosis, and I agree with you that histologically psoriasis could probably not be entirely excluded.

SUMMARY

(1) A case of mycosis fungoides is presented.
(2) Mycosis fungoides may follow in the wake of any chronic scaly erythrodermia.
(3) Biopsies show epithelioma of the hand, and mycosis fungoides.
(4) B.A.L. may have been a placebo, but the itching in this case has disappeared since its administration.

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4 MONTGOMERY, H., and BURKHART, A. J. (1942) *Arch. Derm. Syph.*, **46**, 673.
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Dr. James Sommerville: There are two forms of approach to the treatment of this case. One is a nitrogen mustard preparation and the other is "shower bath" X-ray therapy. For the former I have an intense dislike, and the results are unsatisfactory. The second has to be undertaken with very great care because it is extremely severe on the patient. These patients have to be "hit" hard enough to produce a very sharp blood reaction. Four equal fields are taken, to each field up to 200 r is applied, and the blood count checked daily. When a certain stage is reached I have no doubt that the patient will improve clinically very markedly for quite a time, depending on the extent to which he can stand up to therapy. The first case of the kind, reported by me in the *British Journal of Dermatology* thirteen years ago, is still alive and in good health. The man has survived two attacks of exfoliative dermatitis.

The President: What is the advantage of using a high kilovoltage?

Dr. Sommerville: The kilovoltage used is 150–200. The high kilovoltage acts more quickly. We have used lower kilovoltages but have not got the same results.

Dr. Brian Russell: I believe that the local application of thorium-X is the treatment of choice until tumours develop, when X-rays are usually necessary. Thorium-X keeps the patients relatively comfortable and can be applied with ease and safety to extensive and patchy lesions without the risks associated with X-ray exposure over a wide area.

Dr. C. H. Whittle: Dr. Sommerville has deprecated the use of nitrogen mustard. Reports in the literature vary with regard to the effect of this preparation. Can he tell us more about it? I admit that in asking the question I am thinking also of my own case of ? reticulosarcoma.

Dr. Sommerville: I believe that with more recent methods of using nitrogen mustard it is probably safer than it was in the not too distant past, but in Glasgow we have had one or two abrupt terminations of the treatment, and these have rather frightened me. More recently the results have been better because of the tests carried out beforehand, but I do feel that nitrogen mustard is the last card that should be played. Mycosis fungoides is very radio-sensitive, and results are observed early.

Dr. A. C. Roxburgh: I treated a case of severe mycosis fungoides with malaria during the war. He had about twelve paroxysms of malaria and was pretty ill with it, but his mycosis fungoides cleared up and he was well four years later although not entirely free from eruption.

Morphœa-like Paraffinoma Medicamentosa.—BRIAN RUSSELL, M.D.

Mrs. H. C., aged 58.

History.—At age 19 she had scarlet fever, followed by exophthalmic goitre, for which she received injections on alternate days in the arms. Some time after this, thickening appeared at the sites of injection and has persisted.

At age 24 she had an operation for goitre. Her voice has been hoarse ever since.

At ages 33 and 40 she had pneumonia.

At age 51 she had an operation: right cervico-thoracic preganglionic section, for Raynaud's phenomenon and sclerodactyly.

At age 52 similar operation, left. She also had Trendelenburg's operation to both lower limbs and injection of remaining varicosities.

At age 55 rheumatic pericarditis.

On examination (31.8.49).—Hard, shiny bands of a centrally golden and marginally pinkish colour on the outer aspects of both arms, just above elbow (Fig. 1). Several discrete, pea-sized nodules felt above the bands and a skin-coloured, tender nodule in the vaccination scar.

The patient also suffers from Raynaud's phenomenon, with atrophic changes at the tips of the fingers.

Investigations.—Wassermann and Kahn reactions negative.

X-ray examination—no cervical ribs.

X-ray examination of arms: There are multiple minute opacities veiling the soft tissues of both arms, situated posterolaterally to the lower third of the shaft of the humerus. The appearances suggest that an opaque substance had been injected in these areas (Fig. 2).

Blood count, E.S.R. and serum calcium within normal limits.

Histological report.—Paraffin section (H. and E.): Section shows the dermis to contain a number of clear spaces surrounded by a few chronic inflammatory cells and some fibrous

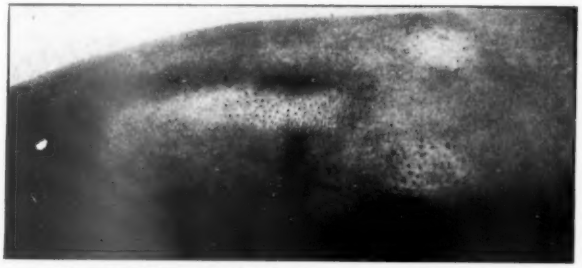


FIG. 1.—Morphœa-like band on outer surface of arm.

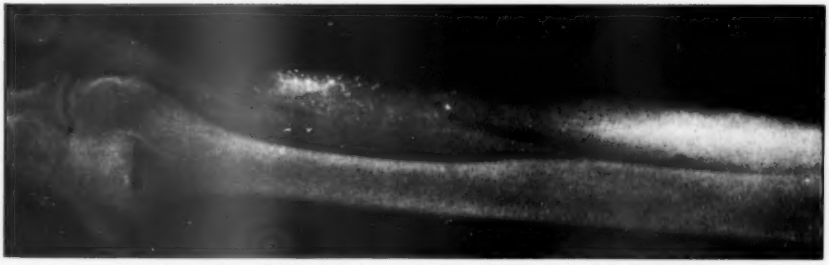


FIG. 2.—X-ray of arm showing multiple opaque globules in hypoderm.

tissue. In addition a number of foreign-body giant cells are seen, some of which contain vacuoles. The histological appearances are those of a foreign-body reaction.

Frozen section, stained with Scharlach R.: Section shows fat droplets in the circular spaces, with marked perifollicular concentrations, also around the sweat glands.

Dr. Russell: Paraffinomata may arise from the cosmetic or therapeutic injection of mineral oil. Vaseline is the more common cause on the face and camphorated oil on the arms, thighs, and breast.

This patient was seriously ill with exophthalmic goitre when she was given these injections, probably camphor in a mineral oil, or an iodized oil. Mook, W. H., and Wander, W. G. (*J. Amer. med. Ass.*, 1919, **73**, 1340–1341) described camphorated oil tumours and their clinical and histological appearances with illustrations to which this patient closely corresponds. The reaction is said to become noticeable first about one month after the injection.

Microscopically there are oval and round cavities, fibrous bands and multinucleated cells, the so-called "Swiss cheese" picture. The injected substance, although at first a discrete mass, is soon split into small parts by the growth of connective tissue trabeculæ into it. A similar histology has been reported in the lungs from the inhalation of oils used in nasal sprays, or from the accidental inhalation of liquid paraffin (paraffin pneumonia).

Miliary Acneiform Tuberculide, with Recent Mantoux Conversion.—BRIAN RUSSELL, M.D.

Miss J. D., aged 29. Nursing sister.

History.—May 1949, noticed a non-itching eruption on the forehead, cheeks and chin.

On examination (4.10.49).—There were semi-translucent, pin-head, yellowish follicular lesions, some flat, others slightly raised, on the chin and cheeks and to a lesser extent the forehead. There were no comedones (Fig. 1). The chest and back were clear. A tentative diagnosis of lymphocytomata was made.

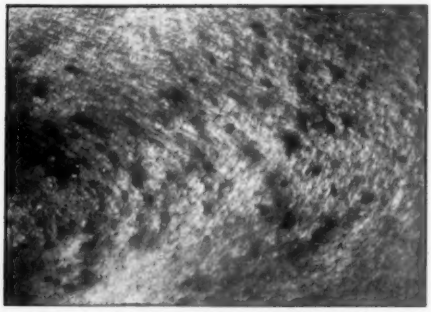


FIG. 1.—Semi-translucent lupoid nodules on side of chin.

Personal history.—Is an only child. Father has pulmonary tuberculosis.

It is known that in 1946 the patient's Mantoux reaction was negative.

December 1948: She suffered from anorexia and loss of weight.

February 1949: An X-ray of the lungs revealed an inexplicable shadow in the right lower lobe which was not found on re-examination.

April 1949: The Mantoux reaction was found to be positive.

Investigations (18.10.49).—Mantoux examination 1: 100,000 positive (erythema 1 inch by ¾ inch, with slight thickening at forty-eight hours).

E.S.R. : 3 mm. in one hour.

X-ray of chest : No abnormality detected.

Histological report (Dr. G. Cunningham, 15.10.49).—Section shows the presence of a follicular granulomatous reaction in the dermis in which giant-cell formation can be seen. There is no evidence of caseation and the Ziehl-Neelsen section is negative for tubercle bacilli. While a diagnosis of Boeck's sarcoidosis is a possibility, the histological picture suggests that a tuberculide or lupus vulgaris is more likely.

Porokeratosis of Mibelli.—H. T. H. WILSON, M.R.C.P.

Mrs. E. B., aged 51.

Family history.—Father alive and well. Mother died—coronary thrombosis. 6 sisters and 1 brother alive and well. 1 brother killed in a mining accident. No family history of skin disease.

Past history.—Measles and whooping cough in infancy. Scarlet fever when aged 18. Edentulous—all upper teeth removed when aged 19, lower teeth removed when aged 39.

History of present complaint.—The present lesion began about ten years ago as a small, slightly painful fissure at the left corner of the mouth. It has since enlarged very slowly and now presents as a semicircular patch of atrophic skin extending outwards and upwards from the angle of the mouth, and inwards for a short distance on to the buccal mucosa. A narrow horny ridge surrounds the atrophic area and separates it from the normal skin (Fig. 1).



FIG. 1.

Investigations.—Wassermann reaction negative. Meinicke reaction negative.

Biopsy (Dr. Haber).—There is a characteristic parakeratotic plug occupying the whole epidermal part of a sweat duct at the edge of the lesion. The sweat duct itself is dilated and funnel shaped. Towards the centre the epidermis is atrophic and the basal layer slightly hyperpigmented. The upper third of the corium exhibits senile elastosis, dilatation of vessels and mild chronic inflammation. The appendages appear to be normal. Porokeratosis (Mibelli).

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Lupus Erythematosus and Rosaceous Tuberculide.—R. J. CAIRNS, M.R.C.P., for G. B. MITCHELL-HEGGS, O.B.E., F.R.C.P.

Mrs. L. H., aged 56.

History of present complaint.—Six years ago a red, scaly patch about 1 cm. in diameter developed on the tip of the nose. She was seen by Dr. Muende who diagnosed lupus erythematosus and advised the local application of carbon dioxide snow and a course of gold treatment. Under this treatment the lesion cleared until fifteen months ago when the eruption recurred.

About nine months ago an entirely different eruption appeared consisting of small groups of pin-head-sized papules on an erythematous background on the sides of the cheeks and upper part of the sides of the neck. Since this time the erythema has faded but the papules have persisted and are increasing in number.

The general health is good. The menopause occurred seven years ago.

Past and family history.—Nothing relevant; no tuberculosis.

On examination.—On the tip of the nose is a white atrophic scar 1 cm. in diameter with a telangiectatic margin. Above this is a similar area. There is no scaling or follicular plugging. There is a white area in the right lower molar region with ulceration.

Scattered widely over the cheeks, sides of the face and upper part of the neck are closely set pin-head-sized papules, brownish yellow in colour. On diascopy the colour is more yellow.

There is no evidence of erythema, pustulation or telangiectasia in association with these papules. The centre of the face shows no papules. The skin elsewhere is unaffected.

Investigations.—Chest X-ray clear; B.S.R. 10 mm. in one hour; Blood: Hb 100%. Cell count normal; urea 38 mg.%; W.R. and Kahn negative.

Biopsy report.—"The epidermis shows some parakeratosis and there is a decrease in the depth of the rete pegs. In the corium there are foci of necrosis with surrounding endothelioid cells. In these foci there is a loss of elastic fibres. External to the collections of endothelioid cells there are lymphocytes. The latter are also present in relation to small blood vessels of the corium. There are a very few giant cells of the Langhans type in relation to the proliferating endothelioid cells. No acid-fast bacilli seen."

Mantoux—6.7.49 : Negative at 1 : 1,000; 10.10.49: Positive at 1 : 1,000; 14.11.49: Slightly positive at 1 : 10,000.

Treatment.—Calciferol 100,000 units daily. Tabs. Ephynal 50 mg. t.d.s.

Comment.—The interest of this case is that a patient with inactive chronic discoid lupus erythematosus developed what appeared to be clinically a rosaceous tuberculide. Histologically there is necrosis and the lesions are deeper than those in the rosaceous tuberculide. There is, however, no marked tuberculin sensitivity as one would expect with a papulonecrotic tuberculide.

I should like to draw attention, however, to the fact that a rise in tuberculin sensitivity occurred which might be related to the development of a tuberculide.

Pemphigus of the Mucous Membranes with Symblepharon.—LOUIS FORMAN, M.D.

Married woman, aged 68.

Ulceration of the mouth, nose, throat and vulva for five years and of the eyes for eighteen months. She states that a raw area appeared round the umbilicus two years ago which lasted some months. Four years ago there was a raw area on the front of the right shin.

From September 1948 to February 1949 she was in the Middlesex Hospital under the care of Professor A. Kekwick who says: "She showed injection of the conjunctivæ of both eyes with chemosis, intense hyperæmia and superficial ulceration of the buccal surfaces of the cheeks, fauces, and vulva. There was a history of nervous breakdowns in the past. She was observed to rub the affected parts most of the night. The arms were kept in plaster and the eyes covered for six weeks, but no improvement was noticed. She had certain morbid fears of becoming a mental case and in 1948 became mildly delusional.

"It had been thought for some time that the lesions were artefacts and in view of her failure to improve with medical treatment it was decided to do a prefrontal leucotomy. During the succeeding two months there was general and local improvement but she subsequently relapsed."

There is now an almost complete symblepharon, and ulceration of the mucous membrane of the cheeks with areas of bulky pyogenic membrane. There is persistent superficial ulceration of the inner surfaces of the labia, with much complaint of irritation. Nikolski's sign was negative. No porphyrins were present in the urine. Capillary resistance was not diminished.

Although shown under the accepted title of pemphigus of the mucous membranes the case appears to belong to the group of acquired epidermolysis bullosa occurring in aged patients. The differentiation between these two conditions in the aged is often difficult. Thus in epidermolysis bullosa, blisters have occurred in the conjunctivæ and appeared spontaneously on the skin. Positive iodide tests have been reported by Sulzberger in a hereditary case of epidermolysis bullosa. Barber and Gougerot have described patients who presented grouped irritable blisters recalling dermatitis herpetiformis and who subsequently were thought to be examples of epidermolysis bullosa.

The following cases were also shown:

Benign Erythematoid Epithelioma (Graham - Little).—Dr. C. H. WHITTLE and Dr. R. E. CHURCH.

Pustular Psoriasis.—Dr. H. W. ALLEN.

(These cases may be published later in the *British Journal of Dermatology*.)

ADDENDUM

Cases and Discussion on Familial Benign Chronic Pemphigus

pp. 61–65, *Proceedings*, Vol. **43**, February 1950. (Meeting held October 20, 1949.)

The following communication has been received from Professeur H. Gougerot, Médecin de l'Hôpital St. Louis, Membre de l'Académie de Médecine, 26, Boulevard Raspail, Paris:

Profitant du rayonnement du Congrès de Bruxelles-Liège de 1949, je me permets de faire une revendication de priorité au sujet de ce pemphigus. En effet j'ai décrit cette dermatose bulleuse (avec Allée) dans les *Archives Dermato-Syphiligraphiques de la Clinique de l'Hôpital St. Louis* (Juin 1933), **T. 5,** page 255, donc plusieurs années avant Hailey-Hailey (dont la publication est d'Avril 1939) et même avant l'observation allemande de Hübner d'Avril 1937, citée par Balter dans sa *Revue Générale des Annales de Dermatologie et de Syphiligraphie* (*Françaises*) de Juillet 1947 (T. **7,** page 243).

Notre observation était caractéristique: "Pemphigus familial héréditaire congénital; un enfant de quatre ans atteint dès sa naissance, père de 38 ans, cousin germain de son père et le fils de ce cousin, âgé de 19 ans, atteints de la même façon; bulles annoncées par du prurit souvent intense ou par des cuissons; évolution courte de chaque bulle, mais répétition incessante des bulles; frottement et pression facteurs déclenchants."

Section of Radiology

President—S. COCHRANE SHANKS, M.D., F.R.C.P., F.F.R.

Churchill Hospital, Oxford, England

[*November* 18, 1949]

DISCUSSION ON THE CHEMICAL FACTORS MODIFYING RADIOTHERAPEUTIC RESPONSE

Dr. Frank Ellis (London Hospital): Radiotherapy is in its third stage of development. The first stage was one of empiricism both as regards dosage and biological observations. The second saw the establishment of a unit of dosage and the development of physical methods for measurement so that chemical and biological results could be compared. Now we are achieving some degree of understanding of the chemical effects of radiation and a wider knowledge of the way in which radiation has its effects on living tissues. As a result of this increasing comprehension we may hope to use radiation with more insight so that the margin between the tolerance of normal tissues and the sensitivity of malignant cells to radiation may be increased, and we may attempt to condition malignant cells so that they are destroyed by smaller doses of radiation than are now used. The two methods available to us are the adjustment of the time-intensity relations of methods of treatment and the use of chemical substances. Both these devices must be dependent on the mode of action of penetrating radiations.

The action of ionizing radiations is not specific and in aqueous solutions most of the energy is absorbed in the solvent. The number of molecules of solute changed by the radiation is proportional to the number of ion-pairs formed by the radiation and thus to the dose of radiation absorbed (Fricke, 1934; Dale, 1942). This was demonstrated by Dale using purified enzymes in dilute solution and led Allsopp (1944) to suggest that the radiation produced its effect on the enzymes through activation of the water. From the activated water molecules the solute receives the energy which results in detectable chemical change. The presence of some other substance in solution either independent of, or derived from, the original substance may protect the latter from the effect of the radiation, and the amount of change which it undergoes is no longer linearly proportional to the dose absorbed but follows an exponential law as was shown by Dale. He was able to demonstrate the different protective effects of various organic and inorganic substances. With very low or very high concentrations, also, the effect is not proportional to dose because some of the "activated water" does not meet with a solute molecule in the first case, and because an appreciable proportion of the solute molecules is affected directly by the radiation in the second case. The hypothesis that the formation of hydrogen peroxide was the responsible factor was disproved by the demonstration that the yield of hydrogen peroxide when water is irradiated could only take place in the presence of dissolved oxygen, but was not dependent on the amount of oxygen dissolved. Weiss (1944) suggested that the water is decomposed by radiation into hydrogen atoms and hydroxyl radicals, and Lea (1947) has given us quantitative estimates of the relative distribution of the hydrogen and hydroxyl radicals. The important point is that owing to the relatively great distance which an electron travels from the site of ionization, as compared with the path of the positive ion, the resultant radicals are differently distributed and so do not recombine at once to form water. It has been shown (Wegmuller, 1942) that ethylene bromide and also thymonucleic acid can only be affected by radiation in the presence of a certain minimum amount of water representing thousands of molecules of water to each molecule of the dissolved substance. Read (1948) has suggested that if an ionizing particle

passes through a chromosome the separation of charge may give rise to tensions of the order of 10^5dynes/cm^2 along the chromosome which might produce breaks at weak points. Chromosome breaks have been demonstrated histologically and Lea (1946) has demonstrated the validity of the target theory for these effects of radiation although the chemical theory also fits the facts. Perhaps there is no fundamental divergence between the two theories if one assumes that a hydroxyl radical set free within a certain definite neighbourhood of a chromosome is a "hit". In any case Waters (1947) has suggested that a molecule will break, not necessarily at the point of initial absorption of energy, but at its weakest point. He also considers that radicals such as the OH radical might be quickly changed in type so as to have less free energy and therefore more selective action. Reactions with OH, NH, SH and C=C groups are known to occur. Further he does not consider that any active radicals produced outside a cell would enter it. They would react with the cell wall. Nevertheless radiation can produce radicals inside the cell and even by direct action, in an enzyme, which might result in an abnormal type of enzyme giving rise to abnormal reactions. These reactions provide a reasonable mechanism for chromosome changes both visible and invisible, and for cytoplasmic changes both primary and secondary to other changes in the cytoplasm and in the cell membrane. The changes in appearance of cells and their behaviour at mitosis follow on the above changes. Certain specific facts have been observed, both chemical and histological, which might indicate the way in which chemical factors will influence response to radiation. For instance it has been shown (Frilley, 1947) that in addition to the yield of H_2O_2 by radiation of water being increased as a result of the presence of dissolved oxygen, there is also a systematic increase with rise in hydrogen-ion concentration (i.e. increased acidity), and with the presence of reducing substances such as hydroquinone, cysteine and ascorbic acid and a diminished yield in the presence of organic acids. Moreover the irradiation of water containing oxygen results in a higher H -ion concentration. Methylene-blue reduction occurs with radiation and is hindered by the presence of dissolved oxygen (Loiseleur, 1947). Tyrosine, deoxyphenylalanine and certain other substances have been shown to undergo oxidation with doses up to 500,000 r. Deamination of amino acids (glycine, alanine and serine) has been demonstrated (Stein and Weiss, 1948*b*) in the absence of oxygen, resulting in ammonia, aldehyde and keto-acid formation such as result from biological oxidation of such acids by enzymes. Also, the addition of oxygen to benzene rings has been demonstrated under anaerobic conditions as a result of radiation (Stein and Weiss, 1948*a*). These experiments prove the formation of OH radicals in water by radiation. In the presence of oxygen the amount of oxidation is increased. The amount of chemical change in certain reactions can be measured colorimetrically and is proportional to dose over a range from 0–50,000 r (Farmer and Weiss, 1948) suggesting that it might be used for dosimetry. The protective effect of a sulphur atom in a molecule is shown by Dale (1947) in the contrast between the protective action of thiourea and that of urea for carboxypeptidase irradiated in solution. Substitution of the oxygen of urea by a sulphur atom increases the protective effect about 2,400 times. This may be of significance when we consider the importance of sulphydryl groups in biological reactions.

Local biological observations. Mitotic inhibition and degeneration.—It has been shown by Spear and his co-workers that radiation in small doses inhibits mitosis and causes degeneration of cells. The inhibition of mitosis can be correlated with the observation by Mitchell (1943) of the inhibition of the production of thymonucleic acid by the enzymes in the nucleolus as a result of radiation. This seems to be a temporary rather than a destructive effect. The degeneration of cells is presumably due to irreversible changes of unknown nature but Wilson *et al.* (1935) consider that this effect is enhanced in growing tissue with a blood supply and appears at the same time as the blood supply degenerates. They consider that the loss of nutrition is responsible. It may be that this is the case, but the possibility of simultaneous changes occurring in both blood vessels and the tissues they supply, both primarily due to the radiation, is also a possibility as well as degeneration following lack of oxygen.

Diffusible substances.—Following the breakdown of cells the products of such breakdown must be set free in the tissues. Jolles (1949) has shown good evidence for the presence in irradiated tissues of a diffusible substance which tends to intensify X-ray reaction in an irradiated field separated from it by a certain distance depending on the size of the field. This fits in with the experience of all radiotherapists that a larger field, from which the passage of such a substance will be more difficult than from a small one, shows more reaction for the same dose and less rapid recovery for the same reaction than a smaller field. This must be a chemical effect. His attempt by means of a chess-board lead filter, to demonstrate an indirect effect of this substance on cancer tissue, is more open to criticism because there must be lateral scatter into the "protected" areas. Doubtless there is an indirect effect as well,

but whether it is cancerocidal rather than merely inhibitory as is the effect of direct radiation is not proved and seems unlikely.

Catalase has been shown to occur in increased concentration in the liver in malignant conditions in animals and in view of its function in destroying hydrogen peroxide such an increase might so interfere with the body chemistry as to affect the sensitivity of neoplasm to radiation.

Antibodies are chemical substances. It is thought as a result of the work of Fagraeus (1948) that antibodies are produced in plasma cells which are produced by more primitive cells in response to an antigen. It has been shown (R. G. White, 1949) that irradiation, shortly before an antigen is administered to a rabbit, inhibits antibody formation. If given three or four days afterwards, however, radiation does not inhibit the effect of a second dose of antigen in producing a secondary response, suggesting that the primitive parents of the plasma cell are sensitive but that the plasma cells are insensitive to radiation. In view of the plasma cell infiltration occurring around a malignant tumour one wonders if this is possibly an attempt to bring antibodies to the site by plasma cells which are produced by antigen set free by the break-up of treated cells.

Sepsis is, of course, helped by small doses of radiation, but interferes with the response to radiation of malignant disease. It may be that the inflammatory reaction competes with the malignant cells for the available oxygen thus diminishing the sensitivity of the dividing cells to the radiation.

Bean root tips and oxygen.—Read (1948) has shown that with a concentration of oxygen up to ·5 c.c. per litre the sensitivity of the growing root tips of the broad-bean to radiation is increased by increasing concentration of oxygen. This is true for both alpha and X-radiation, but the increase with alpha rays is less in proportion than with X-rays, the roots being about 20 times more sensitive to alpha rays with no oxygen, and 9 times more sensitive with 5 c.c./litre of oxygen and over. The oxygen favours inhibition of mitosis and production of abnormal mitoses also. He considers that the denser terminal and delta ray tracks of X-radiation and the dense tracks of the alpha radiation produce their own oxygen and thus give rise to HO_2 and subsequently to H_2O_2. The lack of oxygen in severe anæmia might affect the response of a malignant tumour to radiation.

Other substances.—Sulphonamides and other substances which may be given for other purposes might conceivably have an effect on the local response of a treated lesion.

Kelly (Kelly and Dowell, 1942) in his work on gas gangrene demonstrates a difference which is statistically significant indicating that X-rays and sulphonamides together give worse results in gas gangrene than X-rays or sulphonamides only.

Synthetic vitamin K and a series of acridine compounds have been shown to inhibit mitosis. The latter have also been shown to produce nuclear and cytoplasmic degenerations. Nitrogen mustards, trypflavine, urethane, acetone, carcinogens and the sex hormones have been shown (Hohl, 1948) to cause chromosome fragmentation, nuclear pyknosis due to accumulation of thymonucleic acid and injury to the centromere in cells and the changes are said to resemble those due to radiation. It has been suggested that nitrogen mustards cause chromosome bridging by a chemical linkage of two chromatids (Goldacre, Loveless and Ross, 1948) and that X-rays might do the same by oxidizing two S=H groups in adjacent chromosomes. Many of these substances, however, are toxic and are unlikely to be very effective in dealing with malignant disease because of the vulnerability of other dividing cells in the body.

The least toxic are the sex hormones and synthetic vitamin K.

Suggested application of the above chemical factors.—The cell is by evolution a relatively invulnerable structure. The nucleus of the cell is its least vulnerable part. The only difference between a normal and a malignant cell is in the urge of the latter to grow and divide, irrespective of the chemical restraint of surrounding tissues. Because of these facts I see little prospect of destruction of cancer cells by chemical substances given systemically without the destruction of other dividing cells in the body. Given in safe doses I expect growth restraint only. Radiation is likely to be the most selective agent because it can penetrate to the nucleus of the cells. As a first essential, therefore, we must aim at using radiation as effectively as possible.

Time intensity relations.—The effect of radiation on tissues is to damage all cells some of which break up or otherwise set free a substance or substances which are damaging to the organism and to the tissues in contact with it. The break up of cells and the amount of diffusible substance set free are both proportional to the dose. The aim must be to give a maximum number of röntgens to the malignant cells and to keep the concentration of diffusible substance to a minimum.

The diagrams show the possible behaviour of a toxic diffusible substance resulting from 1 fraction daily compared with 4 fractions daily: (*a*) with incomplete recovery between fractions (Fig. 1); (*b*) with complete recovery between fractions (Fig. 2).

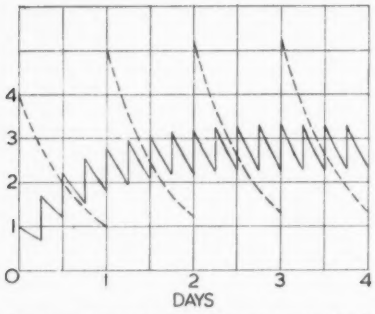


FIG. 1.—Type of cumulative concentration in the tissues of diffusible substance if disappearance of the substance between treatments is not complete. ("Half-life" = $\frac{1}{2}$ day, i.e. $\mu = 1{\cdot}38$.)

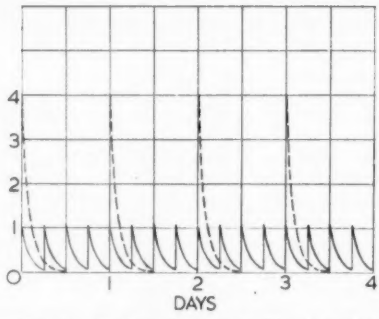


FIG. 2.—Similar diagram to Fig. 1 to show the relative concentrations if disappearance is complete. ("Half-life" = $\frac{1}{10}$ day, i.e. $\mu = 0{\cdot}17$.)

The toxic effect will depend on the concentration reached by the substance at any time and on the product of the concentration and the time for which it is present. The former is measured by the height of the curves in the diagrams and the latter by the area below the curves. It is seen that if recovery is complete the difference is one of concentration only (Fig. 2). If recovery is incomplete there is, in addition, a difference in dose of diffusible substance (Fig. 1) which is present, however, only during the first few days of the treatment. The concentration of the diffusible substance must always be less if there are more fractions, and the higher concentration is more toxic than the low one and is present for a longer time. Therefore the damage done is likely to be greater for the same röntgen dose. This may account for the slighter effects seen on normal tissues with protracted fractionation methods than with simple fractionation and with continuous or interrupted gamma ray treatment, requiring long exposure with low dosage rate, than with the high dosage rate of X-ray treatment. Thus by multiplying the number of fractions it should be possible to give many more röntgens. Gray's hypothesis (1944) suggests that for four times the number of fractions twice the dose can be given, i.e. instead of 4,000 r 8,000 r in one month. This hypothesis is related only to chromosome breaks. It is likely that the formation of a diffusible substance modifies the reaction, resulting in diminished tolerance with increased area and increased tolerance with increasing fractionation.

The larger the volume to be treated, provided one is not treating the whole of the hæmopoietic system, the greater the number of fractions which should be administered for a given röntgen dose.

Protection by radiation against radiation.—In view of the suggested antibody effect it is theoretically advisable to start with small doses of radiation and even possibly to allow an interval of a week or so to enable the antibody mechanism to become active against the tumour.

Radiation in large doses has been shown to protect animals against subsequent radiation. This is not justifiable in the case of human beings—even with the threat of an atomic bomb—unless it is possible to demonstrate that the reaction can be obtained safely. It may be that the production of a chemical substance in the skin is a factor in the protection and that some degree of immunity might be afforded by giving safe doses of non-penetrating radiation to the skin only. This possibility should be explored.

It is a not uncommon experience of radiotherapists to find that seven to ten days' rest from treatment of a patient, who at the end of one week's treatment appears to be tolerating a bath treatment badly, enables the patient to complete treatment to a high dose (e.g. 3,000 r in five weeks to the whole abdomen) without difficulty.

Giving chemical substances.—*Oxygen* is the obvious substance to use in view of the effect on the radiosensitivity of the bean root. I have injected hydrogen peroxide into the middle of a necrosing malignant gland which cleared up completely following a course of radiation. The injection was given just before treatment on each occasion.

Read's experiments show that the maximum sensitizing effect of oxygen is reached at

a tension of 5 c.c./litre. The following calculation shows how this might be attempted in the tissues:

In normal arterial plasma the oxygen dissolved is 0·3 c.c./100 c.c. = 3 c.c./litre. *Tension* = 90 mm.Hg.

Normally in the tissues the oxygen tension = about 40 mm.Hg.

∴ Dissolved oxygen = 1·3 c.c./litre in tissues.

In view of Read's work it seems that an increase in the amount of dissolved oxygen may increase all sensitivity to radiation.

By giving 90% oxygen during treatment, tension in alveolar air = about 700 mm.Hg. Tension in arterial blood = ? 630 mm.Hg, i.e. 21 c.c./litre.

Amount dissolved in tissues = ? 7 c.c./litre.

This will tend to increase the oxygen content at the site of malignant cells, especially when the blood supply is poor.

Hydrogen-ion Concentration

Higher H+ concentration causes increase in H_2O_2 production in water. Whether this can be influenced significantly is doubtful but CO_2 given with oxygen might help.

A meat diet (Paterson *et al.*, 1948) increases general sensitivity to radiation of mice and also tends to produce an acidosis. Whether this would apply to tumours also remains to be seen.

Synkavit.—Mitchell (1948) has shown a significant improvement in advanced cases of cancer treated with large doses of synthetic vitamin K in conjunction with radical and palliative X-ray treatment. The idea behind the method was by using a chemical substance to try to block the synthesis of nucleic acids by a different mechanism from that by which radiation does so. The substance causes inhibition of mitosis in tissue culture of fibroblasts and although gross structural changes are considered to be those of most importance in killing cells by radiation, the combined effect of the radiation and synkavit indicated significant reinforcement of the effects of radiation by the synkavit.

Clinical trials in 240 patients with various types of advanced malignant tumours showed that the compound, which is of low toxicity, is best given as daily intravenous injections. In 130 cases it was given intramuscularly and in 110 cases intravenously. Focal pain or focal sensation in the region of the tumour were a common result of large intravenous doses. Mitchell attributes this to temporary cell œdema. Clinically a small but useful improvement in palliative results is shown by about one-quarter of all the cases of advanced cancer treated by this method and a small but significant increase in survival time with X-ray treatment in inoperable histologically proved cases of carcinoma of the bronchus. Retrogression of tumour cells has been demonstrated histologically by synkavit alone in certain cases of adenocarcinoma. Using ultraviolet photomicrography it has been shown to produce chromosome fragmentation different in appearance from that produced by X-rays. Mitchell and his group have used tissue culture methods to study the antimitotic activity of other substances and it has been shown that the mitotic inhibition produced by some quinones and maleic acid parallels the interaction with –SH compounds. It seems to me that this compound synkavit might inhibit mitosis by a selective blocking of important chemical –SH groups in the cell and that it might help the effect of X-rays by preventing these –SH groups from "protecting" the substances in the cells on which the effect of X-rays is most damaging. As already mentioned, thiourea has been shown by Dale to be very protective and it contains a sulphur atom, its only difference from urea which is a very inefficient protector.

Other substances which act as protoplasmic poisons such as urethane, nitrogen mustards and acridine derivatives might also have an effect on malignant cells which would reinforce the effect of X-rays. Certainly, in the doses in which they have commonly been used, hitherto, it would be folly to try to combine them with radiation, but there is room for clinical experiment with smaller non-toxic doses so that the essential body tissues such as hæmopoietic tissue are not unduly affected. Laboratory investigations of the type being directed by Professor Mitchell would indicate whether these substances offer any hope of an action similar to that of synkavit. Professor Mitchell told me that synkavit-treated cases tend to develop an early severe reaction with X-rays. My experience with patients who have developed such a fierce early reaction with X-ray treatment only is that they do much better than one would expect—and that with a dose only about half of the usual intended dose of radiation. It may be that such patients have in their tissues some such chemical sensitizer. Two at least of such patients who recovered completely from extensive lesions, with no obvious residual normal tissue changes, were very much addicted to beer. Following up such a clue might be worth while.

As in all biological work, clinical radiotherapy is a very difficult subject in which to be sure of a true comparison between cases. Because of this, conclusions are hard to draw, except from large series of cases, but even these must be carefully watched. Synkavit is

not a common vitamin to be given routinely, but many of the other vitamins (especially pyridoxine) are commonly administered for radiation sickness. We cannot say definitely whether they have any effect on the radiosensitivity of tumours. Again, the powerful antibiotics such as sulphonamides and penicillin might have more far-reaching effects in this respect than we have hitherto supposed. The important point which arises here is that, to ensure that wrong conclusions are not drawn subsequently from the statistical analysis of results, the exhibition of certain substances known to have important specific effects on living tissues should be carefully recorded in the radiotherapy notes in adequate detail, and also a record of the hæmoglobin during treatment should be kept because of the possible importance of oxygen. It is essential that controlled tests should be carried out to evaluate the effect, if any, of the many substances which may be administered to patients as supposedly without effect on radiosensitivity.

Hormones are in a similar position. They are all produced normally and a balance is maintained between the various endocrine secretions. The maintenance of this balance is thought to be the function of the pituitary gland.

We all know that a thyrotoxic patient has a more radiosensitive skin but we know nothing about the relative radiosensitivity of tumours in the presence of excess of thyroxin.

The administration of testosterone and synthetic œstrogen is a useful method of influencing some malignant growths, especially of the breast and the prostate.

I am reasonably sure that stilbœstrol improves the response of some tumours to radiation; a useful factor in dealing with ulcerating breast cancer. But the effectiveness of both testosterone and stilbœstrol diminishes as they continue to be used. It seems that this might be partly, at any rate, due to the controlling influence of the pituitary. How may such influence be established and used to help us in treating cancer? The growth hormone originates in the eosinophil cells of the pituitary and may influence cancer growth. No one knows if it has any influence on sensitivity to radiation of the malignant cells. Döderlein of Munich used to irradiate the pituitary routinely in treating cases of cancer of the cervix uteri (League of Nations publication on Carcinoma of the Cervix) and a case has been mentioned to me in which irradiation of the pituitary improved the radiosensitivity of a tumour (Binnie, pers. comm.). Some technique for testing the effect of such substances and procedures clinically is obviously required. Methods which suggest themselves are tissue culture and bean roots in the laboratory, and the use of P^{32} uptake as an index of growth activity in clinical work.

Chemotherapy of cancer has been developed during recent years and so far has been disappointing. I think this is inherent in the nature of the nucleus of the cell and the similarity of malignant and normal cells. Malignant cells differ only in the fact that they multiply with no regard for the needs of the body as a whole and the nucleus of any cell is likely to be relatively invulnerable to chemical substances so that a permanent, complete systemic destruction of cancer by such substances seems to me improbable. There is a case for combining radiation with effective chemotherapeutic substances which might enable adequate destruction of cancer in larger volumes with smaller doses of radiation than are necessary without such reinforcement.

The general effects of radiation due to, and influenced by, chemical factors are a very important aspect of this subject but it cannot be dealt with in this present discussion.

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Dr. L. A. Elson (Chester Beatty Research Institute, Royal Cancer Hospital): *The influence of the protein content of the diet on the response to radiation of tumours in the rat.*—These investigations of the effect of diet on the response of tumours to radiation were the outcome of the discovery that the body growth- and tumour growth-inhibitory action of carcinogenic chemicals is profoundly influenced by the protein content of the diet (Elson and Warren, 1947; Elson and Haddow, 1947; Elson, 1948, 1949). In rats maintained on a 20% protein diet, injection of the carcinogen usually has little immediate effect on body growth, but a delayed action generally resulting in rapid loss of weight which may lead to the death of the animal often occurs later. Animals maintained on a 10% protein diet, however, usually show an immediate growth-inhibitory response to treatment with the chemical.

Implanted Walker Rat Carcinoma 256 shows a similar effect of diet on its response to growth-inhibitory chemicals. This effect is seen most strikingly in a type of experiment in which the inhibitor is administered in a single dose given about twenty-four hours after implantation of the tumour and the animals killed about fourteen days afterwards, the tumours being then dissected out and their weights compared with those of similar tumours in control, untreated animals. In one experiment of this type, using the carcinogenic, growth-inhibitory 2′-chloro-4-dimethylaminostilbene (150 mg./kg.) the average tumour weight in a group of 9 control animals maintained on a 20% protein diet and killed eleven days after the tumour implantation was 12·2 grammes whilst the average tumour weight in the treated groups was 11·4 grammes. Thus little tumour-inhibiting action of the compound is observed in animals maintained on this high protein diet, the ratio of the average weight of tumours in control animals to average weight of tumours in treated animals $\left(\frac{C}{T}\right)$ being 1·1. In similar groups of animals treated under the same conditions except for being maintained on a low (5%) protein diet the weights of the tumours of the control animals were very little different from those of the controls in the 20% protein diet group, the average weight being 11·6 grammes. The tumours of the treated animals in this 5% protein group, however, showed a very marked inhibitory effect of the chemical and only attained an average weight of 0·6 gramme, giving a ratio $\frac{C}{T} = 19{\cdot}3$ (Elson, 1949). Fig. 1 shows a photograph of the tumours obtained in another experiment with two groups of rats both treated with this same compound,

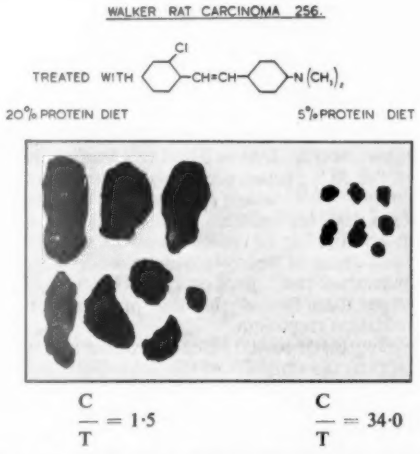


FIG. 1.—Tumours from rats treated with 2′-chloro-4-dimethylaminostilbene (150 mg./kg. i.p.) twenty-four hours after tumour implantation. Animals killed fourteen days after tumour implant.

but the tumours on the left are from the group maintained on a 20% protein diet, whilst those on the right are from the group maintained on a 5% protein diet. (The control tumours which again grew to about the same size in both groups of rats are not shown here, but the $\frac{C}{T}$ ratios are given.) This protective effect of diet has been observed with all types of tumour-inhibiting chemicals so far tested, including the so-called "radiomimetic" substances such as the nitrogen mustards, and suggests that the cause of their growth-inhibiting action may be an interference with the availability or with the synthesis of proteins necessary for growth.

Little is known of the actual mechanism of protein synthesis, but it has been suggested that it may be closely linked with nucleic acid metabolism (Caspersson, 1947). Following this suggestion it was found that the growth-inhibiting hydrocarbon 1 : 2 : 5 : 6-dibenzanthracene when injected into rats caused an increase in the ratio of pentose nucleic to deoxypentose nucleic acid in the liver, as a result of a fall in concentration of the latter (Elson and Harris, 1947).

An initial decrease in cellular deoxypentose nucleic acid was found by Stowell (1945) after X-irradiation of transplanted mouse mammary carcinoma and Mitchell (1942) from investigations of human tumours treated by X-radiation considered that an effect of the radiation was to inhibit the conversion of pentose nucleic to deoxypentose nucleic acid.

There appears therefore to be considerable similarity between the action of chemicals and radiation in this respect and an investigation of whether the profound effects of diet on the response of tumours to chemicals are also evident in their response to radiation appeared to be of considerable practical and theoretical importance. A preliminary study has now been carried out in collaboration with Dr. L. F. Lamerton.

Whole body X-radiation.—A first experiment was to try the effect of whole body radiation on rats implanted with Walker Carcinoma 256 under conditions approximating to those used in the experiments with chemicals. With a daily dose of 100 r per day for eight days the ratio $\frac{C}{T}$ when the rats were killed after eleven days was 2·9 for the group maintained on the 20% protein diet and 5·7 for the group receiving the 5% protein diet.

A similar greater response of the tumours in those animals receiving the low protein diet was thus also observed in the radiation treatment although the actual degree of inhibition was not as great as can be obtained with some chemicals.

The great advantage of X-ray treatment, however, is that it can be applied directly to the tumour in doses much larger than could be tolerated if applied to the whole animal, and the effect of diet under conditions which approach more nearly to those used in radiotherapy of human cancer comprised the main part of the investigation.

Direct irradiation of established tumours.—For these experiments the tumours were allowed to grow untreated for six days after implantation. Daily estimates of the size of the tumours were then made by measurement with calipers along two axes at right-angles. The estimate of the area (sq. mm.) obtained by multiplying these two figures was plotted against the number of days after implantation to show the progress of growth of the tumour.

For the radiation experiments tumours were selected which had reached approximately equal sizes (350 mm.^{2}–450 mm.^{2}—six days after implantation).

Control tumours in animals maintained on both high and low protein diets thus selected usually grow to a size of about 2,000–3,000 mm.^{2} in seventeen to twenty days when death of the animal occurs.

A total dose of radiation of 4,000 r was used and, in the first experiments, this was applied in daily doses of 250 r. The results (Fig. 2, *from* Elson and Lamerton, 1949) show, in the group of 4 animals maintained on the 20% protein diet, only a slight retardation of tumour growth compared with that of controls. The average survival time of the animals was twenty-eight days compared with nineteen days for controls. The group maintained on the 5% protein diet showed almost complete inhibition of tumour growth for a considerable time but eventually the tumours developed areas of necrosis which usually become infected but growth may be resumed before the death of the animal occurs. The average survival time, forty-four days, was considerably longer than that of the high protein group. No animal in either group was cured by this radiation treatment.

The dosage rate was then increased to 400 r per day whilst still maintaining the total dose at 4,000 r. Under this treatment the tumours of the animals maintained on the 20% protein diet at first grew more rapidly than those of the 5% protein diet group. Soon, however, these 20% protein diet group tumours ceased to grow and began to decrease in size and in 3 out of 5 animals eventually regressed completely by a "shelling-out" process. The other two showed partial regression but eventually grew again. In the group of animals maintained on the 5% protein diet only one tumour out of 5 regressed whilst the others grew at a much reduced rate, eventually resuming a more rapid growth rate before causing death.

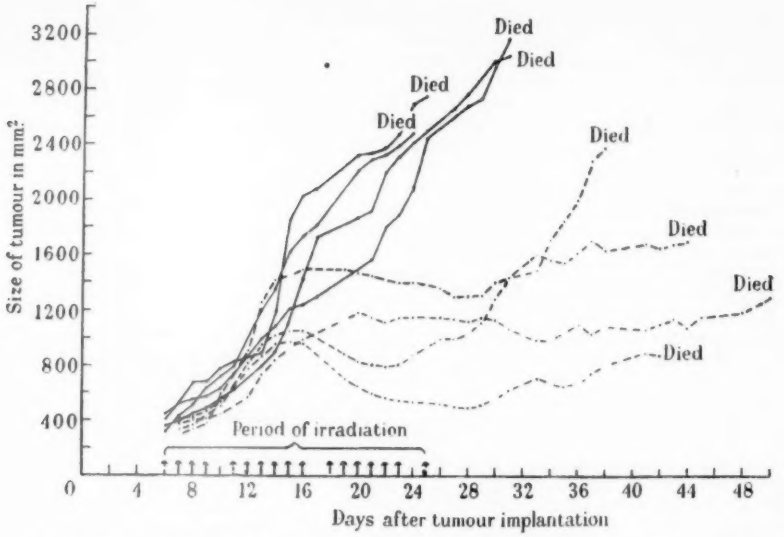


FIG. 2.—Growth of Walker Rat Carcinoma 256 treated with X-radiation; 250 r per day, total dose 4,000 r.

Continuous line Rats fed on 20% protein diet.
Interrupted line Rats fed on 5% protein diet.

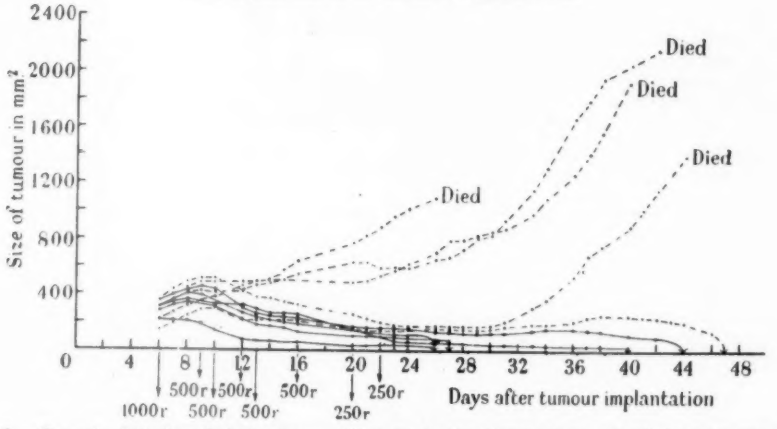


FIG. 3.—Growth of Walker Rat Carcinoma 256 treated with X-radiation; extended treatment with initial high dose (1,000 r); total dose 4,000 r.

Continuous line Rats fed on 20% protein diet.
Interrupted line Rats fed on 5% protein diet.

Figs. 2 and 3 are reproduced by permission of the Editor, *British Journal of Cancer*.

It seems therefore that although the growth-retarding action of radiation may be greater when the animals are maintained on a low protein diet, the degree of tumour regression and ability of the animal to rid itself of the tumour may be favoured by a high protein diet.

This idea was pursued in experiments increasing the daily dose rate to 600 r and changing the diet of the 5% protein group to 20% protein at the commencement of radiation. A daily dose of 600 r over seven days (to keep the total dose at approximately 4,000 r) was found, however, to be approaching the limit of tolerance of the animal for the radiation and the period of treatment seemed to be of too short duration for complete control of the

tumours. Some fractionation of the dose was therefore indicated and it was found that the best method of fractionation was as follows: 1,000 r – – 500 r, 500 r – – 500 r, 500 r – – 500 r – –, 250 r – – 250 r (– – represent two days on which no treatment was given). The total dose of 4,000 r was thus spread over eighteen days. The result of an experiment with this fractionated dosage is shown in Fig. 3 (*from* Elson and Lamerton, 1949). The large initial dose (1,000 r) appears here to have such a strong inhibiting effect on the tumours that a marked difference is no longer observed between the initial response of low and high protein diet animals. The effect of the high protein diet on the process of tumour regression and on the ability of the animal to rid itself of the tumour now becomes the most important factor in deciding the response of the animal to treatment.

In this particular experiment all animals maintained on the 20% protein diet were cured compared with only one cure in those maintained on the 5% protein diet. From a number of experiments with this fractionation technique used on tumours of a similar size and growth rate, complete regressions have been obtained in nearly 90% of the animals maintained on the high protein diet, but in only about 15% of those maintained on the low protein diet.

These experiments suggest therefore that to secure the most favourable response of the Walker rat carcinoma to radiation a primary necessity is suitable fractionation of the dose. The subsequent behaviour of the tumour may then be determined to a very large extent by the nature of the diet of the animal.

In considering this dietary effect one must separate to some extent the processes which determine (*a*) the initial response of the tumour, and (*b*) the elimination of the inhibited tumour and cure of the animal. Process (*a*) is found to be favoured by a low protein diet and process (*b*) by a high protein diet.

By suitable fractionation of the dose, however, it is possible to apply direct to the tumour a first dose of radiation sufficiently high to bring about an adequate initial growth-inhibitory response even in animals maintained on a high protein diet, so that the subsequent outcome of the treatment then depends almost entirely on process (*b*) and a favourable result is thus to a very large extent dependent on a high protein content of the diet.

The question now arises of the nature of this effect of high protein diet and here a wide field of investigation is opened up, whether for instance a certain type of protein (casein has been the main dietary protein used so far) or any of its constituent amino-acids are particularly concerned and whether other nutritional or hormonal factors can contribute to the effectiveness of the treatment.

Investigations of this nature are therefore being carried out in which the weight and food intake of each animal are recorded daily together with the progress of the tumour.

Since the radiation treatment has an inhibiting effect on the growth of the whole animal

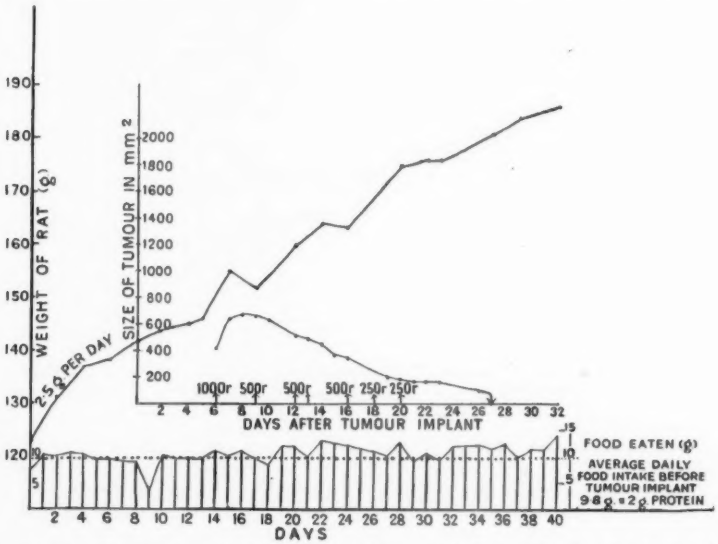


FIG. 4.—Growth of Walker Rat Carcinoma 256, weight, and daily food intake of animal maintained on a 20% protein diet and treated with X-radiation, fractionated doses, total 3,500 r.

as well as on the growth of the tumour, the end-result depends not only on the tumour-inhibiting action of the radiation but also to a considerable extent on the capacity of the animal to withstand deleterious effects. In some cases it appears possible that it may even depend in the first place on the ability of the animal to regain quickly or surpass its normal daily food intake after each treatment.

Thus in Fig. 4 the first (and largest) dose of radiation caused only a slight loss in weight of the animal and very slight diminution in food intake. The animal quickly recovered and thereafter during the whole of the period of radiation maintained an average daily food intake rather higher than its daily average before implantation of the tumour: this animal was cured. The rat represented in Fig. 5, however, showed a diminished food intake immediately follow-

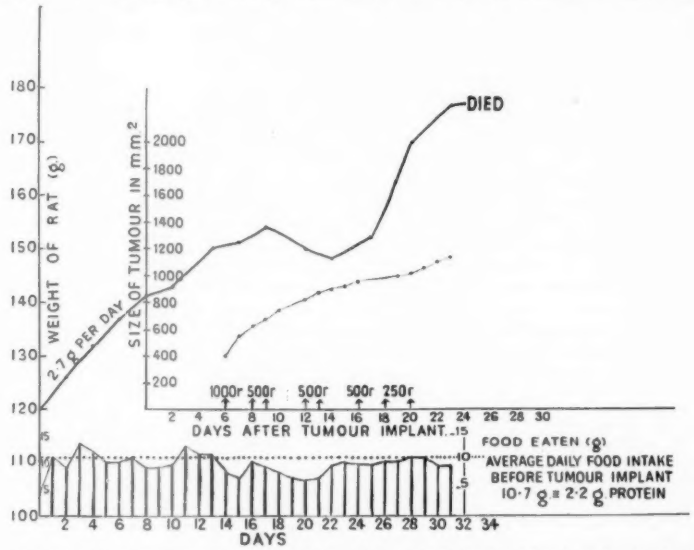


FIG. 5.—Growth of Walker Rat Carcinoma 256, weight and daily food intake of animal maintained on a 20% protein diet and treated with X-radiation, fractionated doses, total 4,000 r.

ing the first radiation treatment and during the whole period of treatment never regained the daily food intake of 10·7 grammes which was its average in the period before tumour implantation. This animal was not cured by the radiation treatment.

Such results suggest the possibility that some sort of protein efficiency index may be developed which may act as a guide to the probable reaction of the animal to the therapeutic agent. A more rational approach to the problem of cancer therapy is thus envisaged in which the growth-inhibitory action of the therapeutic agent is applied so that its maximum effects can be directed to the tumour itself, and deleterious effects on the animal minimized by suitable dietary or other means.

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Dr. Benjamin Jolles (Northampton): An enhancement of the effectiveness of the radiation administered to a tumour can be achieved by fully utilizing the indirect effects of radiation, and by allowing to develop in the appropriate manner and time, processes in the irradiated and adjacent neighbouring tissues which lead to the destruction of a tumour and contribute to the recovery and repair of the damaged parts.

In a new method (Jolles, 1949*a*) of treatment of accessible tumours which is a complete

departure from all the existing methods in use, in both fundamentals and technical details, portions of the tumour 1 cm. square are exposed to radiation while other portions of similar area are protected so that important structures remain undamaged and can contribute to repair. After a suitable period of treatment another chessboard sieve, in which the order of opaque and transparent areas is reversed, is used, and the previously untreated areas are exposed while the already treated areas are protected and their recovery not hindered.

The time factor, which in the conventional radiotherapeutic methods is related to the cell life-cycle and to the attainment of the highest tolerable dose with the avoidance of damage to the skin, in the alternating chessboard method assumes a new complexion. It is to the recovery period of connective-tissue fibres, fibroblasts, &c., that prime consideration in the distribution of the dose of radiation is given.

The sieve method permits the histological study of the various reactions taking place in normal and malignant tissues, and the study of the relative importance of these various reactions in the radiation response of tumours.

In a series of experiments carried out on volunteers, a dose of X-rays was given to two small areas of skin separated by varying widths of untreated protected skin, and the reactions produced were significantly bigger than that over a single area of skin exposed to the same dose of radiation. When, however, the separation between the two paired areas was greater than a certain minimum value, the reaction was equal to that of a single area at a symmetrical site. The separation value which cancelled this reciprocal vicinity effect was, for areas 1·56 cm. by 1·56 cm., approximately 2·5 cm. For areas 2·5 cm. by 2·5 cm. a separation of at least 3 cm., and for areas 3·5 cm. by 3·5 cm. a separation of more than 4 cm. was required to abolish the vicinity effect (Jolles, 1949*b*, 1950) (4 slides shown).

It was previously stated (Jolles, 1941) that, the dose per unit area remaining unchanged, the reaction becomes a minimum when the normal tissues can exert their maximum protective role. In practice, this has proved to be the case in both X-ray and interstitial radium therapy. Introducing the perimeter/area and the shell area/volume ratios, a more comprehensive set of data are at hand when assessing the tolerable and optimal effective doses (Jolles, 1946, 1947, 1948).

The reciprocal vicinity effect of irradiated tissues is brought about by a complex mechanism in which, among others, a diffusible substance produced in the directly irradiated parts might play a role. It is tentatively suggested that apart from the reactivity of the surrounding not irradiated tissues this diffusible substance might be responsible for the events taking place in the parts of tumour shielded from the direct beam.

The hypothesis of a diffusible substance would lead not only to the expectation of the reaction produced by a given dose being less when the area to which it was administered was less, but also to the expectation that a given dose given in a short time would produce a greater effect than the same dose given to an equal area but spread over a longer time by fractionation or by reduction of intensity. For when the radiation is administered slowly the diffusible substance would diffuse away from the irradiated area too rapidly for the necessary concentration for the skin reaction to be achieved.

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Dr. P. C. Koller: The experiments of Dr. Elson demonstrate the importance of tumour-environment in the radiation reaction of the Walker carcinoma. It has been shown that the sensitivity to X-rays can be influenced by diet. While the sensitivity of tumour-cells as measured by the chromosome injuries is the same in animals kept on different diets, the radiation reaction of the connective tissue capsule is more favourable on high than on low protein diet. The histological organization of the connective tissue capsule around the implanted tumour differs on the two diets. It seems that the histological structure and degree of radiation response of the tumour-bed are closely related, and that in the destruction of tumours its role is very important. We have more evidence in hand to show that the reaction of tumour environment to radiation can be influenced by physical and chemical means. The chessboard method of Dr. Jolles, by which the radiation dose is fractionated in time and space and the employment of synkavit by Professor Mitchell demonstrate the practicability of applying this fundamental principle in the treatment of human carcinomata.

Dr. L. F. Lamerton, in reply to a question on the epilation dose, said that the hair of the rats had in fact grown after a total dose of 4,000 r.

[*December* 16, 1949]

JOINT MEETING WITH THE BRITISH INSTITUTE OF RADIOLOGY

The Intensification of the Fluorescent Image in Radiology

By F. I. G. RAWLINS, M.Sc., F.R.S.E., F.Inst.P.

The National Gallery, London

THE method of observing the shadow-pattern cast by a beam of X-rays upon a fluorescent screen, when they pass through an object is well known in medical practice, in industry, and in the fine arts. In all these fields its diagnostic value is considerable, but in the first of them the possibility of excessive dosage is a risk to be taken seriously, and in any case the long period of visual adaptation in the dark is a practical drawback for the observer. So far as industry and the fine arts are concerned, this latter disadvantage remains, with the additional one—not so likely to occur in medicine—that not infrequently it is necessary to examine the object itself in daylight during the course of the fluoroscopic tests, and hence the pre-adaptation is vitiated. Inanimate objects of course need either manual or mechanical moving, or else the apparatus itself must be mobile, which adds to the general complexity. Various schemes have been proposed to achieve these ends, none of them wholly satisfactory.

Thus, there is a real urge to strive for some degree of intensification of the fluorescent image, bearing all these factors in mind. The human eye, though we cannot alter it, is capable of receiving information (and conveying it to the brain) to an extent scarcely realized a generation or so ago, given appropriate physical means.

Mathematical analysis shows that greatly increased brightness can be obtained by optical devices alone if we are concerned with a point-source, or at least extremely limited areas. But this is not so for the case of an "extended scene," that is, when we wish (as we do) to examine a surface comprising say 20 square inches, or something of that order. Then, energy must be brought into the system from outside and this is, in fact, what is done with "brightness intensifiers", two of which will shortly be described. Whatever optical arrangement is used as part of the apparatus, depth of focus will inevitably be lost. Should it be desired to couple a television pick-up tube for remote viewing, or even for further brightness-intensification, the signal-to-noise ratio, important in any case, becomes of greater significance. An effect is to be expected not unlike that experienced in observing at close range an over-enlarged half-tone photograph. Under these conditions, the coarse dot-structure makes the picture almost unintelligible, but across the room this is not so. Actually, as the illumination level is raised, the confusion increases slowly, and therefore the beholder's comfort can be met by providing rather more brightness than is theoretically justified. Furthermore it seems that the human eye possesses the remarkable faculty of "pooling" rod-vision and cone-vision over a fair range of excitation, so that we are not restricted rigidly to the use of rods only or cones only. Also, what has been termed a "variable gain" arrangement permits the build-up of the "message" by successive multiplication rather than by large sudden jumps.

The properties of fluorescent screens may now be reviewed in so far as they influence the main problems. They convert into visible light something like 30% of the X-ray energy which they absorb. Unluckily they only absorb some 15% and therefore the final efficiency is around 3 or 4%, allowing for losses. From this it follows that a "perfect" screen could only enhance the brightness level some thirty-three times or so, whereas, to be of any practical value, we are seeking a step-up of several hundredfold. This demonstrates clearly the magnitude of the effect for which we are looking. Furthermore, examination of a radiograph is commonly conducted at a brightness level of around 30 millilamberts whereas fluoroscopic work is carried out at an illumination of between 0·0001 and 0·001 millilambert, compared with the threshold for photopic vision of about 0·01 millilambert. At such low figures, the eye's discrimination for fine detail (line and contrast) is much enfeebled, which adds yet another reason for amplication of the fluorescent image in practice. It should perhaps be borne in mind that the long period of dark-adaptation needed at present adds very perceptibly to the responsibility of the observer, to make sure that he is, in fact, fully conditioned before beginning an examination at such low brightness levels as may easily be encountered in unfavourable cases.

Intensification Apparatus

An electronic tube, due to Dr. Coltman (1948) of the Westinghouse Corporation U.S.A., consists of a series of phosphors by means of which light is converted into electrons, which are accelerated by the application of a suitable high potential, and impinge upon another phosphor for re-conversion into visible light. The focusing is by means of electrostatic lenses, similar in principle to those used in the electron microscope. The initial brightness-gain of some twenty times is increased by a special optical system by a factor of twenty-five making a total step-up of 500-fold. As at present designed, this tube is 15 inches long, and 7·5 inches in diameter, and the field of view is a circle 5 inches in diameter.

A different device, constructed at Chicago for Dr. Moon (1948), comprises a scanning tube, the X-ray beam passing through a minute pinhole on to a specially constructed fluorescent surface situated in a spherical " collector." A photo-electric current is generated, amplified, and brought to a kinescope in such a way that by the use of synchronous currents a shadow-image is produced. More than one kinescope can evidently be used if desired.

In general, it should be remembered that the observer will need to position himself axially with respect to the tubes in the former case, and that in the latter the use of X-ray units of very high power is implied. These considerations introduce problems of a practical kind into which it is inappropriate to enter here : enough has perhaps been said to show the potentialities of amplification of the fluorescent image in radiology.

This paper will be published *in extenso* in the *British Journal of Radiology*.

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Section of Orthopædics

President—NORMAN CAPENER, F.R.C.S.

[*November* 1, 1949 *contd.*]

? Cavernous Angiomata.—V. M. FRANKLIN, F.R.C.S.Ed.

Patient, a school teacher, aged 32.

First seen in June 1948 complaining of pain in her back which she dated to the birth of her baby 17 months previously. She had been under the care of a gynæcologist and general surgeon who, during investigations, discovered a tumour formation of the third and fourth lumbar transverse processes—the tumour also involved the body of the third lumbar (Fig. 1).



FIG. 1.—Showing collapsed body of third lumbar vertebra with tumour formation of third and fourth left transverse process and the right ala of sacrum.

At this stage the patient was referred to the Orthopædic Department. Further X-rays showed that the right ala of the sacrum was also involved.

The tentative differential diagnosis was then: (1) Multiple cavernous angiomata; (2) Giant-cell tumour; (3) Multiple myeloma.

Investigations.—Blood count normal. Bence-Jones protein negative on repeated examinations. Sternal puncture normal. Acid serum phosphatase normal. X-ray of other bones of the skeleton negative except for a questionable small defect in the parietal region.

Treatment.—Deep X-ray and corset.

I am showing this case first to ascertain whether my provisional diagnosis of cavernous angiomata is correct, and secondly as to whether any other treatment can be suggested. She is a young, healthy woman, putting on weight; in her corset she is completely free of pain and is unwilling to have an operation unless it is essential. She wishes to have another child but I have advised against this. Brailsford mentions 9 cases in the literature of cavernous angiomata of the spine, of which 7 have died from compression of the cord.

POSTSCRIPT.—When seen in April, 1950, the patient was still perfectly fit.—V. M. F.

A member from Edinburgh said that he had recently seen a case with similar X-rays which proved to be a myelomatosis, and other members suggested a diagnosis of myelomatosis in the present case.

The President said that against the diagnosis of myelomatosis was the age of the patient, 32, but he had recently had to operate upon a young man aged 26 who had a tumour of the twelfth dorsal vertebra with paraplegic symptoms and the lesion resembled a cavernous angioma. Microscopy, however, showed a plasmacytoma.

In the present case the absence of Bence-Jones proteose did not negative the diagnosis, because in 30% of the cases of plasmacytomatosis it was absent. Moreover it was more commonly found in the later rather than in the earlier stages. Perhaps Mr. Franklin would report the case again to the Section later.

[*December* 6, 1949]

Stenosis of Carpal Tunnel, Compression of Median Nerve and Flexor Tendon Sheaths, Combined with Rheumatoid Arthritis Elsewhere.—L. S. MICHAELIS, M.D.

The patient to be described provided an opportunity of studying the surgical and pathological problems set by this rare condition and offered clues for the answers to four questions: (1) The cause of compression; (2) its pathogenesis; (3) its site; (4) the cause of "weakness" of flexion and extension of the fingers, mentioned but not explained before.

Miss G., now 59, a former dancer and dancing teacher with well-developed muscles, did strenuous manual work during the war, particularly in an aeroplane factory early in 1944.

Part of her work consisted in stretching stiff canvas material tightly over frames. This she did mainly with her right hand, the left meanwhile steadying the frame.

Within a few months she suffered from attacks of intense pain shooting from her right palm into the tips of her fingers. The pain subsided intermittently but returned after renewed effort. Since the end of the war all light manual work, e.g. knitting, led to numbness and "pins and needles" in palm and medial fingers.

In 1944, also, the fingers of her left hand swelled, several joints becoming and remaining thickened and showing temporary stiffness but no ulnar deviation.

In 1948 both shoulder-joints became temporarily painful and stiff. The left joint recovered soon, but the right swelled to double its size and remained permanently enlarged and tense. Movement was limited, pain not severe.

In the last six months movements of the fingers of the right hand became more and more difficult, without any visible changes in the fingers. The flexor tendons appeared to be caught at the wrist. The ulnar two fingers in particular were found, on waking up, to be either maximally flexed or extended. And it took the patient a long time and much pain in the palm to straighten or bend them. In the effort of trying to do so, "lumps" appeared above and below the carpal ligament and there was here a crunching feel and noise on movement. Within the last few months a hard small swelling formed over the flexor aspect of the distal joint of the right thumb. It was tender to touch and interfered with her ability to grip.

The patient was highly strung, very apprehensive and depressed, under treatment for high blood-pressure and "nerves" for a long time.

On examination the lesions already described were found. No other joints were involved, the general condition was good, the B.S.R. 11 mm. in first hour, 25 mm. in second hour. X-rays showed no bony changes in the right shoulder, the cervical spine or either hand.

The sensory disturbance in the median distribution was severe but its outline was blurred. There was no motor paralysis but slight paresis and wasting of the thenar muscles on the right. On the left there were no neurological signs or symptoms.

Diagnosis.—Rheumatoid arthritis—in a silent stage—of left fingers and right shoulder. Stenosis of carpal tunnel with compression of median nerve and flexor tendon sheaths right.

It was decided to (1) split the transverse carpal ligament, (2) remove the hard body on the thumb, (3) open and wash out the right shoulder-joint.

Operation (L. S. M.).—General anæsthetic.

(1) Bunnell incision over the right palm (*see* Fig. 1). The distal end of the tendon of m. palmaris longus and the proximal half of the palmar fascia were exposed and the tendon transversely divided. The inner—or dorsal—surface of the palmar fascia showed the strands of the normal insertion of the palmaris longus at the superficial surface of the transverse carpal ligament, spreading out fan-wise over its distal half to its distal margin.

The median nerve, proximal to the proximal margin of the carpal ligament, was found to be over twice its normal width and resembled a tendon in being yellowish and glistening with œdema of its sheath.

Under vision throughout the carpal tunnel was opened in the mid-line. The cut surface of the carpal ligament showed the following changes: From the proximal edge to half-way distally the ligament was about 1 to 2 mm. thick, elastic and of normal appearance. Its distal half, corresponding to the extent of the palmaris longus insertion, was thickened to 4 mm., rigid, and the cut surface stippled with whitish-yellow spots. These spots closely resembled, in miniature, the necrotic foci seen in the diseased tendon of the supraspinatus.

Within the distal half of the carpal tunnel the median nerve was diminished in size, assuming further distally its normal thickness. The tendon sheaths of the flexor tendons were not thickened but, distally to the distal edge of the ligament, filled with clear watery fluid.

When the ligament had been completely split, extension and flexion of all fingers were free. The fluid in the tendon sheaths now flowed back proximally. The skin was sutured.

(2) From a Bunnell angle incision (*see* Fig. 1) the hard body over the flexor surface of the end joint of the thumb was removed. It had what at first appeared to be a thin capsule from which it was easily released. The joint was not opened.

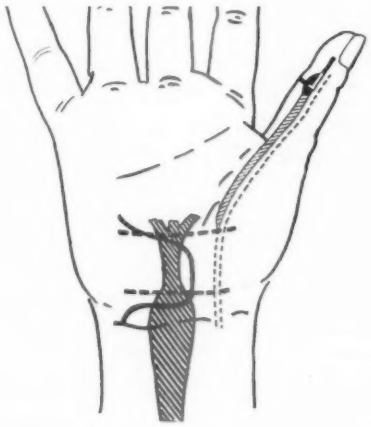


FIG. 1.—The two incisions used:—(1) in the palm; (2) over the distal flexor crease of the thumb.

See also:—
Position of carpal ligament; compressed median nerve; effusion and loose body in sheath of flex. poll. lg.

(3) From a 2 inch incision 1 in. lateral to the delto-pectoral groove the capsule of the right shoulder-joint was found to be tense and bulging with fluid content. On opening the joint about 60 c.c. of straw-coloured fluid escaped, containing many fibrinous flakes. The synovial membrane was much thickened, dark red, and further fibrinous material could be removed from its surface by washing out (1 eusol in 10 saline). The opening of the capsule in the upper part of the front of the joint was intentionally not sutured to allow drainage of the reactive effusion into the soft parts—a valuable procedure. Muscle and skin were sutured.

The patient made a smooth recovery, the freedom of movement of the fingers and absence of pain being noticed at once. On removal of stitches on the eighth day all wounds had healed. There had been, during the first few days, leakage of effusion-fluid from the lower angle of the shoulder scar and—this was not at first properly understood—from the thumb incision.

Pathological investigation of the fluid from the shoulder-joint showed it to be sterile.

The hard body from the thumb was sausage-shaped and over 1 cm. long. It had a firm smooth surface. The pathologist, finding many giant cells in a collagen stroma, called it a giant-cell synovioma (*see below*).

Discussion.—Our patient has several points in common with those mentioned in the literature:

A middle-aged woman, hard manual work to which she was not accustomed, signs of compression of the median nerve cured by splitting the transverse carpal ligament. With Russell Brain's and two of Newman's cases she shares the absence of bony changes which might have explained compression by exostosis encroaching on the tunnel-floor (Fig. 2A).

The lesion was one-sided, as in Woltman's and Zachary's second cases, in contrast to all others. The special manual strain fell on her right hand only.

Our patient differs from all those previously reported by showing this condition to be part of or coinciding with rheumatoid arthritis elsewhere.

She also had symptoms and signs of involvement of the flexor tendon sheaths which, if it was present in earlier cases, was not described or used to explain the "weakness" of finger-movement. The hard body from the thumb will be found to be part of this aspect of the condition.

Incision and approach to the transverse carpal ligament (Fig. 1).—The centre two-fifths of Bunnell's extensile incision for the palm of the hand permit wide exposure without causing a painful scar or keloid. (Bunnell, S., *J. Bone Jt. Surg.*, 1932, **14**, 27, *see also* Michaelis, L. S. Atlas Orthop. Operations, London, p. 32, Fig. 27C).

There is no valid reason to confine oneself to a remote approach from the lower end of the forearm. Any incision ending at the distal crease of the wrist prevents anything but blind splitting of the ligament in its distal half which, as we hope to show, means that the surgeon is bound to miss the crucial feature of the pathology.

Operative findings.—Anatomy: The operation afforded an opportunity to see how the insertion of m. palmaris longus grips the distal half of the carpal ligament. Contraction of this muscle pulls this part of the ligament palmarwards and removes the distal edge from nerve and tendon sheaths. At the same time the roof of the carpal tunnel is stiffened, is more resistant to pressure and better fulfilling its duty as a protector of the nerve. Part of the insertion of m. flexor carpi ulnaris lifts in the same manner the ulnar half of the proximal part of the carpal ligament (Fig. 2B, 3, 4).

This action, particularly of the palmaris longus, appears to have been overlooked so far. Besides tightening the palmar fascia and to a negligible extent helping to flex the wrist, the muscle is a tensor and levator lig. carpi transversi.

Where, as is common, the muscle is absent, the ligament cannot be tensed. But neither can the pathological condition be produced which is responsible for compression. There is no need to abandon the practice of using its convenient tendon for plastic operations.

When the palmaris longus muscle and tendon are taut, the distal mouth of the tunnel is opened. It appears that the position of wrist and fingers needed to make the tendon stand out differs slightly in different people according to minor anatomical variations. In my own wrists the tendon is most prominent (1) with wrist and fingers strongly flexed, (2) with wrist flexed 20 degrees and fingers hyperextended (Fig. 4).

In any other position of either wrist or fingers the tendon is either less taut or fully relaxed, e.g. if the wrist is sharply flexed but the fingers straightened, the tendon relaxes.

Maximal flexion of wrist and fingers at once appears to throw the greatest strain on the muscle. This is a position used when we pull and tightly grip, as in the present case, a canvas-sheet. This position also is often reached in washing and wringing laundry.

The significance of these facts for the pathology of carpal stenosis will become evident in the next paragraph.

Operative findings.—Pathology: (1) *Changes in the carpal ligament.* We have seen that its proximal half showed a normal appearance. The distal half, however, was greatly thickened, rigid and, on the cut surface, beset with necrotic foci (Fig. 2B).

These foci not only suggest comparison with those seen in the diseased insertion of the supraspinatus tendon; they are the same condition in a much smaller structure, brought about by the same agent, continuous and forcible muscle-pull on a tendinous sheet. In both cases fibrous tissue in the middle-aged, showing signs of beginning vascular changes, is affected in the same manner.

Certainly in our case, very probably in all cases where stenosis has not been caused by bony changes in the walls or floor of the tunnel, the cause of compression of the median nerve is to be found in the changes in the carpal ligament whose distal half was thickened, rigid and showed multiple necroses.

(2) *Changes in the tendon sheaths.*—The presence of effusion in the flexor tendon sheaths distal to the distal margin of the carpal ligament shows that stenosis is not confined to the proximal edge of the ligament but actually most pronounced at the distal edge.

Effusion was most noticeable in the sheath of flex. poll. long. which lies close to the radial bony wall and in the superficial plane, together with the nerve and the flexor sublimis tendons. The connexion between this effusion and the hard body removed from the distal flexor crease of the thumb occurred to me only at the end of the operation when watery fluid escaped from the angle incision. It now became clear that what had been assumed to be a "capsule" of the "tumour" was in fact the distal tip of the tendon sheath which had been pushed beyond the flexor-crease by the tense effusion (Fig. 1). The "tumour" was a loose body of the tendon sheath consisting of a concretion of synovial deposit. On the ulnar side, too, the superficial tendons of the fourth and fifth fingers, compressed between the bony wall and the now rigid roof, had been more affected than the central and deep tendons. This explains the selective limitation of movement of the ulnar fingers.

Conclusions.—In a middle-aged woman, suffering from rheumatoid arthritis of the left fingers and right shoulder, carpal stenosis and compression of the median nerve on the right were caused by thickening and rigidity of the transverse carpal ligament (distal half). This in turn was due to occupational overstrain on m. palmaris longus which normally lifts and tenses that part of the ligament. The flexor tendon sheaths, particularly of the flexor pollicis longus, were occluded at the distal edge of the carpal ligament. And a loose body had formed from deposits over the distal joint of the thumb.



FIG. 2A.—Carpal tunnel. Palm up.

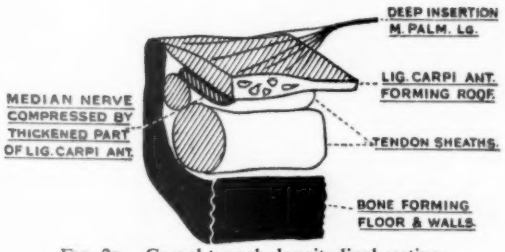


FIG. 2B.—Carpal tunnel: longitudinal section.



FIG. 3.—M. Palm. Lg.: deep insertion into distal half of Lig. Carpi Ant.
(*Superficial insertion into carpal fascia not shown.*)

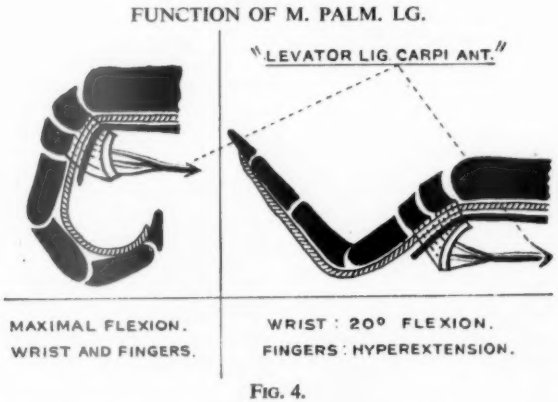


FIG. 4.

These changes in the roof of the tunnel explain compression in the absence of changes in its walls or floor which could be held responsible for the stenosis. "Increase in pressure within the tunnel" may well have been due to changes in the roof as here described. They could not have been seen as long as a remote approach was used. For future cases, free exposure by Bunnell's incision is recommended.

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Arthrography of the Shoulder-Joint.—A. W. LIPMANN KESSEL, *M.B.E., M.C.*, F.R.C.S.

Introduction.—A study of the gleno-humeral joint by contrast-medium arthrography was carried out at St. Mary's Hospital, London, during the past two years because it had become apparent that some new technique of investigation must be developed if we are to advance our understanding of some of the many common shoulder disabilities.

The principal object of the work was to standardize the technique of arthrography, to learn what are the normal features of an arthrogram and to see whether it has any value in the diagnosis of injuries to the musculo-tendinous cuff. We also hoped that the investigation might shed some light on the pathology of the so-called "frozen shoulder".

This short paper is based on 25 satisfactory examinations and is preliminary to a full report which will be given to the International Radiological Congress in 1950 by my colleague in this work, Dr. D. H. Nelson, who was responsible for all the radiology.

Literature.—The use of arthrography in the diagnosis of injuries to the shoulder was first suggested by Codman [1], who stated that he was unable to obtain any useful diagnostic results. Oberholzer [2, 3] in some unconvincing work, claimed to demonstrate the capsular lesion in dislocation of the shoulder. The method, however, has only been fully developed in Stockholm, first by Lindblom and Palmer [4, 5] and more recently by Oliver Axen [6]. They are very enthusiastic about its possibilities. At last year's autumn meeting of the British Orthopædic Association, Withers [7] mentioned the use of arthrography of the shoulder-joint. In view of the fact that his report published in a recent issue of the *Journal of Bone and Joint Surgery* is the only reference to the subject in British literature, I should like to consider it at some length: "In establishing the diagnosis" (between complete and incomplete ruptures of the supraspinatus), "there is a place for arthrography", he says and he claims to do this by injecting perabrodil into the subdeltoid bursa. "It can then be demonstrated in a few minutes whether or not there is a communication between the bursa and the joint cavity."

Our experience does not lend support to this view. Unlike Withers, I have found it quite impossible deliberately to inject the subdeltoid bursa unless it is distended by an effusion. Indeed we regard it as indicative of an effusion if a bursogram is accidentally obtained. Furthermore we do not think that the interpretation of the films is so simple that, as Withers says, "It can be demonstrated in a few minutes whether or not there is a communication between bursa and joint."

If Withers' criterion for the diagnosis of a ruptured supraspinatous tendon is accepted, many patients may be subjected to unnecessary exploration, because coincidental filling of bursa and joint is almost always due to faulty technique, and only rarely and under special circumstances due to rupture of the musculo-tendinous cuff.

Technique.—The needle is introduced under local anæsthesia from a point 1 in. anterior to the acromio-clavicular joint, until its point is embedded in the articular cartilage of the head of the humerus. It is then slightly withdrawn while pressure is maintained on the plunger of the syringe. It is very important to remember that at the site of injection there is no more than a capillary joint-space. An important technical factor is the choice of a suitable needle; almost without exception failures are due to the use of a needle which has too long a bevel. It is only too easy to inject dye into the joint, the bursa and related soft tissue planes at one and the same time. I have found a child's lumbar puncture needle to be the most suitable.

At present we use 8–10 c.c. of 35% pyelosil. We discontinued the use of oily solutions because of some unpleasant reactions; our experience of air-arthrography is too small to give an opinion.

We followed Lindblom's advice on radiography which calls for some complicated positioning and at least 6 different views, but it is probable that one can get all the required information from two views: the first taken immediately after the injection while the patient is lying supine with the needle still in situ, and the second a good joint-space view taken at right-angles to the plane of the scapulo-humeral joint.

It is essential to do the injection under screen control if one is to be certain of the subsequent interpretation of the films.

The normal arthrogram is shown in the line drawing (Fig. 1) and radiograph (Fig. 2).

FIGS. 1 and 2.—The normal arthrogram.

[I]. A thin superior meniscus which outlines the articular cartilage on the upper half of the humeral head. Its precise limitation at the anatomical neck of the humerus indicates integrity of the musculo-tendinous cuff.

[II]. Delineation of the synovial sheath of the tendon of the long head of biceps.

[III]. Well-marked filling of the subscapular bursa.

[IV]. A pool of dye in the inferior joint recess.

Arthrograms of abnormal joints are shown in Figs. 3–7.

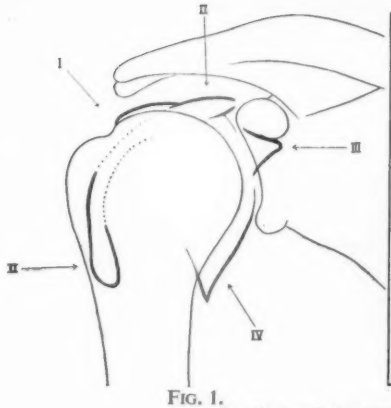


FIG. 1.



FIG. 2.

The Normal Arthrogram (Figs. 1 and 2).



FIG. 3.—Subacromial bursogram in a case of traumatic bursitis.



FIG. 4.—"Frozen shoulder"; note the obliteration of the inferior joint recess.



FIG. 5.—Rupture of supraspinatous tendon. The meniscus extends beyond the confines of the joint.



FIG. 6.—Rupture of supraspinatous tendon. Serial X-rays show progressive leak from joint into bursa.



FIG. 7.—Osteochondromatosis of shoulder-joint. Case shown to Orthopædic Section by Addison, J., on October 4, 1949 (*Proc. R. Soc. Med.*, 1950, **43**, 112).

Evaluation of the method.—I have not shown any examples of acute or recurrent dislocation, or ruptured long head of biceps. There are numerous such examples in the European and Scandinavian literature—50 of Lindblom's original 107 investigations were on patients suffering from rupture of the long head of biceps, but I think this can only bring discredit on the technique because it laboriously establishes what is already known by clinical observation.

In the diagnosis of supraspinatus injuries, Lindblom states that: "The value of the clinical signs is limited and relative . . . but arthrography, if properly carried out, provides exhaustive information regarding the existence of the rupture, its type, site, &c."

From our experience we cannot, as yet, share his enthusiasm but I am sure arthrography has a useful place in selected cases.

We examined 3 patients who displayed the "frozen shoulder" syndrome, and in each we found a degree of obliteration of the inferior joint recess. (May this not be secondary to almost *any* lesion which causes a stiff adducted shoulder?) We found no evidence to support the view of Nevasier [8] who states that adhesions exist between the synovial membrane and the head of the humerus, or the idea put forward by Lippmann [9] that the underlying lesion in a "frozen shoulder" is bicipital tenosynovitis.

Conclusion.—Using 35% pyelosil, arthrography of the shoulder-joint is usually, but by no means always, painless if a completely intra-articular injection is made. There are, however, occasional unpleasant reactions and the routine use of the method must carry certain risks. We cannot at this stage recommend arthrography of the shoulder as a routine investigation—as it is used, for instance, in congenital dislocation of the hip-joint—but once the technique is standardized it should prove helpful.

During the course of this work it has naturally given rise to some ideas about disorders of the shoulder region. I should like to end with some general remarks which, although they do not arise directly from the subject of this paper, may be of some interest:

I think that many so-called supraspinatus disorders are really disorders of the acromio-clavicular joint.

It is probable that the cause of the "frozen shoulder" syndrome will often be found elsewhere than in the gleno-humeral joint.

And finally, I believe that the gleno-humeral joint is a singularly blameless structure, and is much maligned.

In conclusion I should like to thank Mr. V. H. Ellis without whose encouragement and helpful criticism this work would not have been carried out. I also thank Dr. Cardew of St. Mary's Hospital, Clinical Photographic Dept., for the preparation of the slides and photographs.

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Section of Surgery

President—DIGBY CHAMBERLAIN, Ch.M., F.R.C.S.

[*January* 4, 1950]

DISCUSSION ON TREATMENT OF ACHALASIA OF THE CARDIA

Mr. N. R. Barrett: Our topic is one about which there are important divergences of opinion and I shall be surprised if my observations meet favour. They are based upon a group of 40 patients who have attended my Out-patients Department for periods in excess of a year.

First let us agree to define the scope of our subject and to use the term " achalasia " which, in the present state of our ignorance, is synonymous with " cardiospasm". These words describe a clinical entity in which there is a prolonged subacute obstruction situated at the lower end of the œsophagus, but without an organic stricture. I submit that we are not discussing those states of temporary or transient spasm induced by emotions such as fear or excitement, or by demonstrable pathological lesions such as carcinoma of the stomach, peptic ulcer, cholecystitis, &c.

The differences between "primary achalasia" and these secondary conditions of spasm cannot always be diagnosed by the radiologist or even the endoscopist, for the shape of the column of barium which the former studies and the configuration of the lumen of the gullet which the endoscopist scrutinizes, are often identical in true "achalasia" and in spasm. But at operation the external appearances of the gullet are pathognomonic. Spasms, induced by pathological conditions, relax under anæsthesia; but in "primary achalasia" the findings are constant and typical: the point at which the œsophagus actually enters the stomach is normal (I hesitate to call this "the cardia" because by placing metal clips at the junction of the squamous and the columnar epithelium, Allison has demonstrated that what looks like "the cardia" through an œsophagoscope may be shown, upon subsequent fluoroscopy to be situated at some distance from the clips placed at the junction of the gullet and the stomach at thoracotomy). Immediately above the cardia there is a segment of gut, approximately 4 to 6 cm. in length, which is about the shape of my little finger. Apart from its compactness and its smallness, the narrow segment is, in all other respects, normal ; that is, there is no evidence of inflammation, no adhesions, no increase in vascularity and no constant abnormality *vis-à-vis* the nerve supply, the crura of the diaphragm or the liver tunnel. It is agreed that the first inkling of achalasia is often increased irritability of the whole gullet below the aortic arch, and that this is soon associated with subacute obstruction focused at the lower end. Which of these two is the cause and which is the effect is not settled; nor is it known what sets the ball rolling. Above the obstructing segment the changes in the walls of the œsophagus are comparable to those found in the colon in Hirschsprung's disease; but it is not wise to carry the analogy further at the moment because the pathological changes which are said (Bodian, M., Stephens, F. D., and Ward, B. C. H., *Lancet* 1950 (i), 19) to be a constant feature in the recto-sigmoid segment—namely, complete absence of ganglion cells from the intramural plexuses and the finding of numerous non-medullated nerve bundles with supporting cells in the customary sites of the intramural autonomic plexuses—have not been found by all authorities in achalasia: nor are the problems of treatment comparable.

The changes in the dilated part of the gullet are proportionate to the duration and the completeness of the obstruction, and however distorted and inflamed the upper œsophagus may become it is my experience that the lower constricting segment takes no part in these changes. One other observation is relevant to treatment, namely that despite severe clinical obstruction it is always possible to pass an instrument into the stomach provided only that the way can be found.

In suggesting that the discussion be limited to the treatment of "primary or idiopathic achalasia" I stress that, as achalasia and carcinoma occur in the same age groups (Fig. 1),

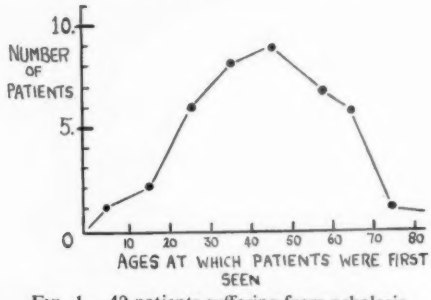


FIG. 1.—40 patients suffering from achalasia.
NOTE.—Many of these patients come within the carcinoma age period.

there will be occasions when only thoracotomy can settle the diagnosis; and as regards achalasia itself that there are often no clinical methods of gauging the existence or the progress of the disease. I have records of several patients who, upon their own statement, are in good health but in whom a barium swallow reveals distension and distortion of the œsophagus by residue held as high as the base of the neck.

Active treatment of any condition is based upon a knowledge of the outcome when nothing is done. In "achalasia" there are those whose disability is slight and who, by a variety of ingenious swallowing and dietetic tricks, and perhaps by the intermittent use of octyl nitrite, can so order their lives that nothing more is necessary. I advocate conservative measures at the extremes of life: in infants the behaviour of the cardia, both anatomically and physiologically, is to me so mysterious that any measure which will gain time—short of surgery—is to be recommended. It is my impression that the disease is more certainly self-limited and self-curative in children than in adults.

In adults the disease may not only have periods of clinical remission—during which the radiological abnormalities seem to persist unaltered—but the patients adjust themselves to a state of permanent sub-normal health and often cannot be persuaded to stake their claim for a chance of cure. They forget what it feels like to be really well.

Others are driven to seek help because the disease and the disabilities progress, and although death from starvation is unusual (because the liquid contents of the gullet are always dripping through into the stomach so that in time decomposing and offensive food becomes available for digestion) life can be rendered undesirable. When the patient has become "œsophagus conscious" and obstruction a permanent entity, the disease is then asocial as well as unpleasant. The victim cannot eat with, or even at the same speed, as others, cannot go out to entertainments, cannot take a holiday and finally does not dare to live.

This disease should be checked early and many believe that, at the outset, psychiatric treatment should be assayed. I take leave to condemn this practice because in my view it adds insult to injury. The treatment is based upon the widely held belief that achalasia is induced by some psychological upset, but for my part I cannot confirm this after careful review of my cases. Further I deny that any clinician can state—except in rare and exceptional circumstances—the moment when the changes in the œsophagus, which precede and account for the clinical manifestations, started. I have records of a ward sister who was at the peak of her active career, and who, during the war, went for a short holiday to a coastal resort. The Germans happened to bomb the place at that time and she received some minor injuries as a result of which chest X-rays were taken and a "large mediastinal hæmatoma" was considered to be present. In good health, but handicapped by a serious diagnosis, she was transferred post-haste to a thoracic surgical unit where it was ascertained that long-standing and advanced achalasia was present. It would be difficult to say when the changes in her œsophagus started. On the other hand I know that most people who develop achalasia have ample reason for becoming disturbed mentally, and that their troubles are speedily alleviated by curing the œsophageal obstruction: that is by placing the horse in front of the cart.

Another treatment, introduced in the seventeenth century, and resurrected in fairly recent times, is the mercury-loaded bougie; this is widely used. These instruments have served their purpose but are obsolete. There is no doubt that some patients not only get relief by regularly

passing a bougie but are happy to do so; for the majority, however, the instrument is repulsive to the patient and revolting to those lay people who find themselves watching the contortions it may necessitate before or during a meal. Moreover, the treatment is often ineffective either because the bougie curls up in the redundant pouch of œsophagus above the diaphragm, or because to achieve success the constricted segment must be stretched more than can be achieved by any instrument which the patient swallows. I damn bougies because they do not cure, because they induce a habit and a gamut of neuroses, and because they defer more effective treatment.

The quickest, the safest and the most certain treatment of the early case is by endoscopic dilatation of the narrowed segment; 60% to 80% of patients can be alleviated of all symptoms and cured in one or two treatments provided an instrument of the type devised by V. E. Negus be used. Success depends upon distending the œsophagus to such a point that the circular muscle fibres are ruptured—namely to a diameter of 5 to 7 cm.—and the surgeon who does this often enough will undoubtedly rupture the œsophagus one day. Rupture of the œsophagus can be corrected surgically, provided the early signs and symptoms are recognized and a diagnosis made. In another paper I have described these clinical features and have successfully diagnosed and treated this complication (Barrett, 1946 and 1947). My second point about endoscopic dilatation is that it is helpful to do the operation with X-ray screening facilities available: in this way the bag can be distended with radio-opaque liquid and the stretching observed and controlled under the eye.

I believe that patients who cannot be cured in this way should be advised to undergo operation without delay. To wait is to invite further deterioration, and as surgeons we are well aware that the chance of curing most diseases is inversely proportional to the time the patient has been afflicted. The majority of my patients suffering from "achalasia" have had dysphagia for five to fifteen years before they come to me.

A great range of different operations have been devised and tested during the last eighty years (Table I) and certain general principles can now be formulated. The failure or success

TABLE I.—OPERATIONS FOR ACHALASIA

Those Directed at the Baggy Œsophagus Itself

1 Excision of strips (Jaffe, 1897; Reisinger, 1907)
2 Œsophago-plication (Freeman; Meyer, 1911)
3 Œsophagostomia thoracica (Zaaijer, 1912)
4 Making the Œsophagus taut (Freeman, 1923)

Those Directed at the Narrow Segment

1 *Dilatation*
  A Retrograde (von Hacker, 1900)
  B Transgastric (von Mikulicz, 1903)
  C Hydrostatic Bag (Plummer) (Negus)
2 *Plastic Operations*
  A Cardiomyotomy (Heller, 1913; Röpke)
  B Cardioplasty
    1 Complete (Meyer, 1913)
    2 Extramucous (Marwedel, 1903) (Wendel, 1910)
3 *Excision*
  Cardiectomy (Rumpel, Pribam)
4 *Deviation*
  Œsophago-gastrostomy (Heyrovsky, 1912; Grondahl, 1916)

Those Directed at the Diaphragm

1 Phrenicectomy
2 Transposition
3 Division of the Crura (Brassler, 1914)

Those Directed at Nerves

1 Vagotomy (Meyer; Sauerbruch, 1921)
2 Sympathectomy (Knights, 1935)

[Modified from the Table in the Paper by A. Ochsner and DeBakey, *Archives of Surgery*, 1940. This paper contains a full list of references.]

of any operation can no longer be attributed to details of technique—for instance a plication of the redundant œsophagus does not fail because silk, as opposed to thread, stitches were used: nor need we discuss the relative merits of laparotomy as opposed to thoracotomy. Secondly, those procedures which have been directed at the obstructing segment itself have

been more efficacious than any others. Thirdly, although *any* operation which overcomes the œsophageal obstruction relieves all the symptoms and the reversible pathological lesions which afflict the patient, an operation which renders the cardia incompetent permits reflux of gastric contents into the lower œsophagus and causes "œsophagitis" in a high proportion of cases. The œsophagus, and especially the squamous epithelium which lines it, is extremely susceptible to gastric juice and is digested like the skin of the abdominal wall around a duodenal fistula. The exact mechanism which normally prevents regurgitation is not clear, since a muscular sphincter is not present, but the probability is that reflux is prevented because the œsophagus enters the side of the stomach obliquely, and this obliquity functions as a flap or valve. The valve effect is enhanced by the diaphragmatic pinch-cock, the fact that the œsophagus is surrounded on three sides by the liver (i.e. the liver tunnel) and by gas which is normally present in the fundus of the stomach. Whatever be the explanation it is certain that œsophago-gastrostomy, cardioplasty, excision of the lower constricted segment and other operations of this type are all apt to be followed by incompetence, reflux and "œsophagitis".

Up till 1947 I had performed 19 œsophago-gastrostomies (Table II). In all these patients the early results were brilliantly successful, and there was no operative mortality; but only 3 appear to me to be finally cured and I live in expectation that they too will develop symptoms one day. The remaining 16 have either had pain, dysphagia due to inflammation,

TABLE II.—ACHALASIA

Analysis of the results obtained in 40 *patients treated by me*

20 had been, or still are, being treated with *bougie*.
- 3 are good results.
- 17 continue bougie treatment or have ultimately been treated in other ways.

19 underwent *Œsophago-gastrostomy*.
- 3 good results.
- 16 imperfect results.

11 underwent *Heller's operation*.
- 10 good results.
- 1 imperfect result.

NOTE.—A "good result" is one in which the patient is symptomatically well at least one year after operation. An "imperfect result" means that the patient still has signs or symptoms of local or general type.

or anæmia due to slow bleeding from the œsophageal mucosa. In some the symptoms—and especially anæmia—have been crippling and persistent; in others disability has been present from time to time, but in all there are radiological or endoscopic changes in the lower gullet and this seems to me to be undesirable. I must remind you that these pathological changes are situated in precisely that reach of the œsophagus which, before operation, had a normal mucosa. The patients themselves would not all express their disapproval in such strong terms, for they are prepared to pay a high price for being able to swallow; but some have had to have other operations to correct the mistake, and one is dead as a result. Some manage to carry on by taking iron or liver injections ; and some by sleeping in the sitting position; some refuse further treatment although they have an anæmia with a hæmoglobin as low as 50%.

In conjunction with R. H. Franklin I have recently published these late results (*Brit. J. Surg.*, 1949, **37**, 194) and he added 6 patients upon whom he had performed a cardioplasty (i.e. an operation in which the cardia and the narrow segment were opened longitudinally and sewn up transversely). 3 of his 6 patients were symptomatically cured, but 4 of these 6 are known to have active "œsophagitis" at present.

You will ask why these serious late complications have not been reported by other surgeons, and I can only assume that the reason is that the patients have not been followed up for a sufficiently long time. In 1940 Ochsner and DeBakey collected 88 examples of œsophago-gastrostomy from the literature and they state that there were 5 deaths and 82 good results. In 1945 Clagett, Moersch and Fischer added some more good results but their patients were only watched for a few months. Kay, writing in 1948, said that "great relief" followed seventeen transpleural cardioplasties, but he does not tell us about his late results. Gill and Child (1948), on the other hand, admit that most of the patients who were followed for six months to two years continued to have untoward symptoms referable to swallowing.

I must stress that of the various inflammations which affect the œsophagus and which are called "œsophagitis" two different types are relevant to this disease. The first precedes any treatment and is due to stagnation of food and saliva above the obstruction; it resembles stercoral ulceration, seen elsewhere in the gut, and often causes persistent pyrexia—pyrexia

of this variety is an indication for early operation; it will disappear as soon as the obstruction has been relieved. The second is the probable late result of most operations upon the cardia and is due to regurgitation of acid-pepsin into the lower œsophagus.

In my opinion two, and possibly three, operations relieve the obstruction without setting the stage for "œsophagitis" but *only one* of these should be practised. The first is transgastric retrograde dilatation—a procedure which was carefully tried out by Sir James Walton in this country and is now regarded as obsolete because it carries a relatively high mortality and morbidity rate and because better results can be had by endoscopic dilatation with the Negus instrument. The second is extra-mucous or intra-mucous cardioplasty and for this procedure good results have been claimed but they do not tally with Franklin's experience which I have already mentioned and therefore I recommend that the operation be discarded. The third is Heller's (1913) œsophago-cardiomyotomy in which the obstruction is overcome by dividing the circular muscle fibres of the lower œsophagus. This leaves the cardia intact and anatomically in its normal position. If the circular fibres are properly and completely severed throughout the narrowed zone the clinical results of Heller's operation are excellent: my own experience is limited to 11 cases all of whom were cured except one very old woman who was much relieved, but whose disease was far advanced. The operation is not followed by regurgitation and this has been verified both by screening the patients in the Trendelenburg position and by showing that neither acid nor pepsin can be found in the gullet. Wulff (1949), who has had experience of this operation, concurs with these observations, and with the fact that occult blood is not found in the stools post-operatively.

Heller's operation is safe; it can be done in a few moments by thoracotomy and the patients should be able, and allowed, to swallow normally as soon as they return to the ward. No complicated after-treatment is necessary or desirable, but any operations performed upon the lower œsophagus are sometimes complicated by a small, late, serous, pleural effusion. In some patients the X-ray appearances are not as satisfactory as the clinical state, but the patients put on weight and are well satisfied.

There are no people more grateful than those whose dysphagia has been cured. Indeed, the results of a successful Heller's operation can be far reaching; it is not unusual for divorce proceedings to be settled out of court, for bags to be packed and the family to go away for a holiday, for father to put on weight and mother to become pregnant.

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Mr. P. R. Allison: I have studied and treated 76 patients suffering from cardiospasm. Of these, 34 were male and 42 female. The onset of symptoms occurred most often between the ages of 30 and 40 years (28%). The next most common decade was 10–20 years (18%), and the third 40–50 years (15%). Owing to the long duration of symptoms in these patients the greatest number of them presented for treatment between the ages of 40 and 50. Quite a high percentage of patients, however, were between 50 and 70 years of age when they first came to hospital for attention.

Three patients were treated over fifteen years ago by gastrotomy and digital dilatation of the cardia. All were relieved of their symptoms. Another patient was treated by spinal anæsthetic and died a few hours afterwards from inhalation pneumonia. As well as this death there have been two other fatalities, one from gross starvation, and one from perforation of the œsophagus and mediastinitis. Neither of these 2 patients had any treatment and were moribund when they came to hospital. A uniform routine of treatment has been adopted in all the other patients. It has consisted of œsophageal wash-outs, followed by œsophagoscopy and dilatation of the cardia through the œsophagoscope by the Negus hydrostatic dilator. When this has not been enough to relieve symptoms, the process has been repeated at least once and sometimes three or four times. Where the œsophagus is greatly dilated it is most important to wash it out and aspirate it before œsophagoscopy, and indeed before any anæsthetic is administered, if inhalation pneumonia is to be avoided. Altogether the Negus hydrostatic dilator has been used in 59 patients, and of these it has been the only line of treatment in 46.

The result in these 46 patients is described as "successful"; the definition of this term will be discussed later. It was unsuccessful in 13. Of the 46 successful patients, 29 were cured by

one dilatation, 15 by two dilatations, 1 by three, and 1 by four. I believe that the success of any method of treatment of cardiospasm depends on rupture of the circular muscle fibres at the œsophago-gastric junction. If this is to be achieved with the Negus hydrostatic bag, it is important that the walls of the bag, when distended, should be parallel, or otherwise it will slip either upwards into the œsophagus or down into the stomach without actually rupturing the muscle fibres at the cardia. The shape of the bag, when distended, depends on the way in which the linen lining beneath the rubber covering is cut and stitched, and this is liable to some variation from time to time and with different manufactures. Some of the failures have no doubt been caused by badly-shaped bags slipping. The success or failure of treatment does not seem to depend very much on the length of time the patient has had symptoms. A patient may have had dysphagia for fifty years and may still be cured by a single application of the bag. One of the most important points about this form of treatment is that it is an out-patient procedure. That a patient who has had many years' dysphagia and regurgitation may be cured of his complaint after one attendance at the out-patient department is a striking tribute to the method. The only complication has been a perforation of

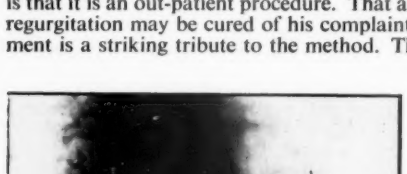


FIG. 1.—Cardiospasm with prolapse of cardia 2½ in. below the hiatus. Œsophagus a huge inert bag.

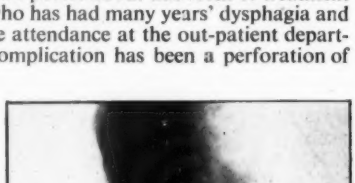


FIG. 2.—Same patient after Heller's operation combined with repair of diaphragmatic hiatus. Œsophagus greatly contracted, but still inert.

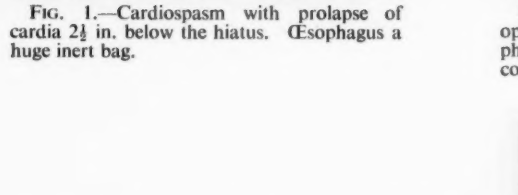


FIG. 3.—Extreme emaciation shortly before death. Starvation from cardiospasm.



FIG. 4.—Œsophagus and stomach removed post mortem from the same patient.

the œsophagus in the neck by the œsophagoscope. This was a complication of œsophagoscopy rather than of the Negus dilator, but it occurred in a patient with cardiospasm who was being treated under a local anæsthetic. Immediately the accident was recognized, the œsophagoscope was withdrawn and inserted into the œsophagus proper, the œsophagus was treated by aspiration and the cardia dilated, after which an incision was made in the neck and the tear sutured. The patient made an uninterrupted recovery.

The only other form of treatment which has been used has been the Heller operation. This consists in the division of the circular muscle fibres at the lower end of the œsophagus and adjacent part of the stomach. It can be done either from the abdomen or from the chest, but in this series the thoracic approach has been used entirely.

The Heller operation has been used in three groups of patients: firstly, for small children, where no great confidence has been felt in the ability to stretch the cardia without causing trouble; secondly, for those patients who have not been cured by the Negus hydrostatic bag; and thirdly, for those patients in whom the œsophagus has become so lengthened and tortuous that the cardia could not be reached either by the œsophagoscope or by the bag. In 2 patients, the inflammation at the lower end of the œsophagus with fibrosis of the œsophageal muscle was so marked that the mucosa was opened during the performance of the Heller operation, and had to be sutured. Of 19 patients treated in this way, the results have been classified as uniformly successful.

The approach to the cardia for Heller's operation has been through the bed of the ninth rib on the left side. After the pleura has been opened and the lung retracted, local anæsthetic is injected into the mediastinum, the mediastinal pleura is incised, and the finger passed round the lower end of the œsophagus. A tape is then passed round this for traction and the cardia is gently pulled up through the hiatus. The affected area is usually not more than $\frac{1}{2}$ in. to $\frac{3}{4}$ in. in length. It is cylindrical on section, and constricted. This area corresponds to that part of the œsophagus which normally lies in the diaphragmatic crural canal. Above it the œsophagus distends, and the wall is greatly thickened by hypertrophy of its muscle layers. A single vertical incision is made through the muscle tissue, starting about an inch above the cardia, and passing down across the cardia on to the stomach for $\frac{1}{8}$ in. to $\frac{1}{4}$ in. This incision is deepened down to the submucosa until the mucous membrane prolapses freely into the wound. The œsophagus is then allowed to retract between the diaphragmatic crura, the chest is closed and the lungs expanded. In one patient, where the hugely dilated œsophagus had prolapsed through the hiatus for about $2\frac{1}{2}$ in. into the abdomen (Fig. 1), it was felt that incision of the muscle in this way might render the lower end of the œsophagus, which was in the abdomen, liable to peptic digestion. In this patient, therefore, after division of the muscle, the cardia was drawn back between the crura, and the crural fibres were lightly stitched behind it (Fig. 2). There have been no patients whose symptoms have not been relieved by one or other of the above forms of treatment, and it has never been found necessary to have recourse to the more complicated operations, such as cardioplasty and œsophago-gastrostomy.

During the course of this discussion the word "successful" has been used in regard to treatment and it is, therefore, necessary to define as far as possible exactly what we mean by the word in this context. Success from the patient's point of view, of course, depends entirely on the relief of his clinical symptoms, but from the surgeon's point of view there are two aspects of this. Firstly, the clinical relief of symptoms, and secondly, the radiological changes. It is also necessary to emphasize that the word "success" must be taken to mean "success within the period of follow-up". Mr. Rock Carling has described a patient who was completely relieved of her symptoms for twenty years, but in whom dysphagia recurred suddenly when she found the lodger with his throat cut over the sink. I, myself, have had one patient who developed cardiospasm after the death of her mother, was completely relieved, and then developed it again on the death of her father. From the clinical point of view, a success is considered complete where a patient can eat normal meals without pain, without a sense of obstruction, without regurgitation, and without medicine. This includes patients who have to eat slowly and who (for reasons which will appear later) have to use fluids to clear the gullet. Success is partial where a patient eats normal diet, but has occasional feelings of obstruction. The gaining of weight and an increase of vigour are also important indications of clinical success. Sometimes a patient's only symptoms are pulmonary, either the result of inhalation of œsophageal contents, or collapse of a lung or lobe, due to pressure on a bronchus by a greatly distended œsophagus. In these patients the criterion of cure is that cough, pneumonic attacks, and pleuritic pains should be abolished.

In referring to the gain of weight on successful treatment, it is worthy of note that there are two main types of patients presenting with symptoms, firstly, the one who has lost a little weight in the beginning, but who subsequently maintains a steady weight and a steady food intake even though there is great retention in the œsophagus, and secondly, the patient who undergoes progressive starvation even to the point of death (Figs. 3 and 4). It is quite

unusual for patients with cardiospasm to be grossly undernourished, and the reason for this appears to be that the œsophagus retains all the food taken and allows it to pass through very slowly by continuous drip feed into the stomach.

The criteria of radiological cure are much more exacting, and it is comparatively rare to see the œsophagus return to normal anatomy and physiology after any form of treatment (Figs. 5 and 6). The degree to which success is demonstrated radiologically, however, unlike

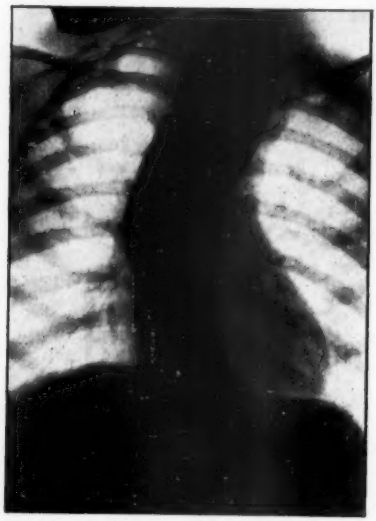


FIG. 5.—Cardiospasm in a child of 3 years. Symptoms since 4 months.



FIG. 6.—Same patient after left transpleural Heller's operation. Normal anatomy and physiology of œsophagus.

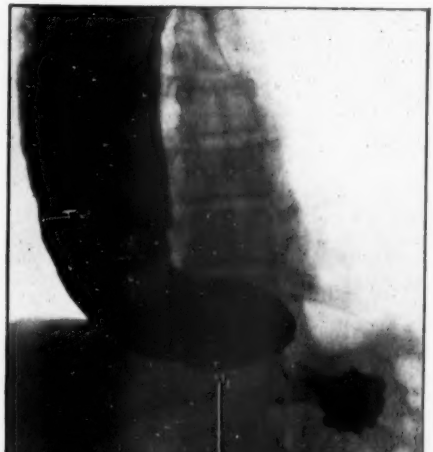


FIG. 7.—Advanced cardiospasm Stage 3 associated with rheumatoid arthritis, œsophagitis and pyrexia.



FIG. 8.—Same patient after Heller's operation. Clinically cured, radiologically imperfect. Some muscle activity present, but completely inco-ordinated. Passage of barium into stomach by gravity and respiration only.

clinical success, depends on the length of time the symptoms have been present, and the amount of dilatation of the œsophagus. Usually the radiological changes after treatment are in the reverse order to those occurring during the progress of the illness. It is, therefore, useful to comment on these. In the early stages of cardiospasm, a constriction with irregular muscle movements is seen in the lower two-thirds of the œsophagus with slight dilatation in the upper third. In the second stage the constriction is seen at the cardia, the lower two-thirds of the œsophagus begin to dilate, but movements, often inco-ordinated, are retained and even increased. In the third stage, constriction is limited to the cardia, and the rest of the œsophagus becomes dilated and passive. If the patient is treated in this last stage, the cardia may be dilated and food pass through the œsophagus by gravity and the force of swallowing, but active movements of the œsophagus are never regained. In such patients the picture of the œsophagus when filled with barium may look very similar before and after treatment (Figs. 7 and 8). In this way it happens that a patient may be completely relieved of his symptoms and be a clinical success, but the radiologist may give a disappointing report, especially if he is influenced by the amount of dilatation of the thoracic œsophagus. The treatment in the first and second stages, however, may result in very marked diminution in the size of the œsophagus, a much more co-ordinated activity, and an active passage of food from the œsophagus into the stomach in addition to that effected by gravity and respiration (Figs. 9 and 10).



FIG. 9.—Cardiospasm passing from Stage 2 to Stage 3.



FIG. 10.—Same patient after hydrostatic dilator.

No description of the treatment of cardiospasm would be complete without some reference to the side-lines of treatment. Chest complications have been found in 16% of the patients and have included bronchitis, pleurisy, paraffin pneumonia, bronchiectasis, lung abscess, and inhalation or pressure pneumonia. The treatment of chest complications is the treatment of the œsophageal lesion, for when this has been effected, the chest is likely to improve, except of course in the case of established bronchiectasis. Rheumatoid arthritis with clubbing of the fingers has been noted in 4% of the patients, and here again it is important not to be misled by the obvious deformities, but to concentrate on the treatment of the cause. In my experience drugs have given little or no benefit. Psychological factors in cardiospasm have frequently been stressed, but there has been very little evidence to suggest that psychiatric treatment has ever been effective in these patients. There is no doubt that most of the patients are "queer", but neither this, nor financial, family, or other worries seem to me to distinguish them in any way from their fellows. The best treatment that they can have, from a psychological point of view, is the relief of their dysphagia, so that they can eat at the family table, go out to restaurants, and mix freely with the rest of the world.

Mr. A. L. d'Abreu (*Birmingham*): Agreeing as I do with Mr. Allison about the ætiology of this condition, I find that although patients appear normal psychologically, the onset in most has followed acute emotional upsets. One patient, a first-class cricketer, suddenly developed symptoms during an important game and these persisted for twenty-three years until he was cured by a cardiomyotomy. Some patients have been extremely intelligent and others have appeared quite stupid; but some children have started their symptoms in the first months of life. In these very young patients progress, whether good or bad, depends largely on the intelligence of the parents and most of the infants maintain their nutrition well. The act of vomiting disturbs them little and I have seen them vomit a meal, but succeed a few minutes later in swallowing one of equal size and quality. Some children have had respiratory symptoms and my experience has been that of the opening speakers inasmuch as a surgical cure of the cardiospasm is invariably followed by improvements in chest condition. In particular, I remember one boy with long-standing cardiospasm who presented himself with radiological evidence of collapse of both lower lobes, which re-expanded after a satisfactory Heller's operation.

In the treatment of these patients I agree with Mr. Allison that the main duty at the first interview is to promise a cure. I dislike the use of Hurst's mercury bougie, and have never seen antispasmodic drugs give good results. If there is difficulty in curing the patients by forcible rupture of the muscle fibres by Negus's dilator, the modified Heller's operation should be proceeded with at once. In elderly patients (three of mine were over 70) it may be preferable to perform this operation without previous attempts at œsophagoscopic dilatation, as often they have an enormous œsophagus and the instrumentation is not easy.

In twelve operations of cardiomyotomy relief has been immediate and continued in all except one. This patient, aged 71, could not remember the onset of dysphagia. The œsophagus was enormously dilated with a large loop passing well into the right side of the thorax (Fig. 1). After division of hypertrophied muscle fibres in the lower portion of the œsophagus

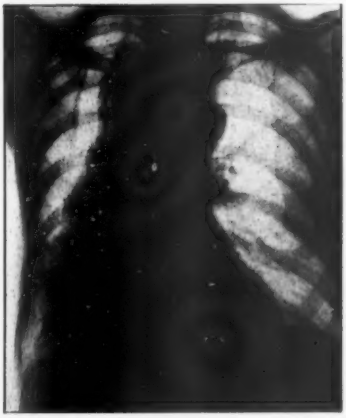


FIG. 1.—A straight X-ray of a grossly dilated œsophagus which extends well into the right thorax. Air can be seen above the clavicle and the sigma dilatation at the lower end reaches to the right cardiophrenic angle.

she was able to swallow anything and gained 1 stone in weight which has been maintained, but she still has occasional obstruction with regurgitation. The œsophagus has not regained its normal peristaltic waves, but possibly the extent of the myotomy was inadequate.

Sir Thomas Dunhill only wished to speak of two operations, and to pay a tribute to the work of the present generation of surgeons. Their spirit of enterprise and their practical achievements have kept pushing farther forward the contributions of surgery in the alleviation of suffering, and have based on secure foundations the treatment of conditions which an earlier generation approached tentatively and without sure knowledge.

Fig. 1 shows an œsophagus the result of cardiospasm which had prevented the patient from swallowing an adequate amount of food for thirty years. It had been treated in the early stages by means of a mercury bougie. The patient stated that this had never given her relief. The illustration shows the position of the bougie in relation to the "S"-shaped curve



FIG. 1.—Mrs. D. 1932.



FIG. 2A.—Mrs. J. 1.11.45.



FIG. 2B.—Mrs. J. After operation, 26.3.46.

of the œsophagus when I attempted gently to pass it. It also shows the impossibility of examining the cardia with an œsophagoscope in this patient. Subdiaphragmatic œsophagogastrostomy was performed in 1933. The patient lived for some years much more happily than before the operation, although the œsophagus did not empty. She died seven years later. She lived in the country and I could not get accurate information of the cause of death.

Two others were operated upon by this method. One reported for some years afterwards and then could not be traced.

Fig. 2A is from a patient upon whom I operated five years ago. She had been unable to swallow adequate nourishment for twenty years, and for a fortnight before operation had been unable to swallow at all. It was necessary to give transfusions for several days, and then a jejunostomy was performed. Following this, with a transthoracic approach, the lower end of the œsophagus was dissected free from the diaphragm at the hiatus. A longitudinal incision was made through the muscle coats of the œsophagus for 2 cm. and continued for a similar distance on to the stomach. Fig. 2B seems to indicate that the diameter of the œsophagus had approached its normal size. This is not so, but it shows that the barium swallow is not held up—it passes through without delay. The patient now eats whatever the family eats, she has gained five stones in weight and is very happy. This is without doubt the better operation.

Mr. E. D. D. Davis: I have the notes of 34 cases of achalasia. Most of them were treated by dilatation through the œsophagoscope. Recently I have had the opportunity of dissecting the normal œsophagus in the full term and other fœtuses. Longitudinal sections have been cut of an 8 and 20 weeks whole fœtus to show the form and relations of the œsophagus. These anatomical and clinical investigations have been carried out at the Ferens Institute of Otolaryngology of the Middlesex Hospital (Fig. 1). The fœtal sections show the deviation of the



FIG. 1.—One of a series of longitudinal sections of the full-length 8 weeks fœtus to illustrate the form and relations of the cardiac end of the œsophagus.

œsophagus to the left and the abdominal or diaphragmatic portion curves slightly from before, backwards and obliquely to form an arch over the aorta. The orifice of the cardiac end of the œsophagus as it enters and blends with the lesser curvature of the stomach is directed slightly backwards. The two domes of the diaphragm dip downwards in the form of a V to enclose the œsophagus and the diaphragm is bound by areolar tissue to the wall of the œsophagus. The left crus of the diaphragm in section is almost triangular and dips into the angle where the cardiac end of the œsophagus deviates to the left. This inward bulge of the left crus cannot be seen with the œsophagoscope. The right crus is flattened and the two crura form a groove or canal for the œsophagus. The caudate lobe of the liver is parallel to and in relation to lesser curvature of the stomach and extends as far as the orifice of the cardiac end of the œsophagus. It is difficult to see how enlargement of the caudate lobe of the liver can press on, or distort, the cardiac end of the œsophagus. Dissections of fresh post-mortem specimens of the cardiac end of the œsophagus show the longitudinal folds of the abdominal œsophagus to be much enlarged and thickened. It is apparent that the prominence of these folds reinforces the closure of the lumen of the œsophagus. The muscular wall does not show any sphincter but the circular muscular fibres are well developed and the

musculature becomes thicker as it blends with the wall of the stomach. The pale pink mucosa of the œsophagus ends abruptly as a clear line where it joins the thick velvety darker red mucosa of the stomach. The magnified sections show a clear line of demarcation between the mucosa of the œsophagus and that of the stomach. When the œsophagoscope passes the upper sphincter of the œsophagus air dilates the passage and the longitudinal folds are obliterated but the movement of the wall with deep respiration can be seen easily. The pulsation of the aorta can be felt and sometimes seen particularly near the cardiac end. At about 40 cm. from the teeth the stellate appearance of the hiatus of the œsophagus as it passes through the diaphragm is observed. Brown Kelly states that when the endoscopic tube is about 3 cm. from the hiatus the lumen rhythmically opens and closes with respiration. This movement is difficult to see and when the œsophagoscope passes through the hiatus the dark red mucosa of the stomach is immediately and abruptly seen. Sometimes regurgitation of gas and stomach contents are seen.

If a normal patient is observed with the X-ray screen swallowing barium cream, the barium cascades from the pharynx and slithers down the œsophagus and at the hiatus the stream of barium narrows. If the patient holds his breath following inspiration and when the diaphragm descends, the barium flow is stopped but it immediately passes into the stomach on expiration with the rising of the diaphragm.

When a patient suffering from achalasia is observed, the globular dilatation of the gullet fills with barium almost up to the thoracic inlet, then the weight of barium seems to force a trickle of barium into the stomach. Arthur Hurst stated that the mercury bougie should contain 1 lb. 5 oz. of mercury. Mosher found that a pressure of 3 lb. to 4 lb. exerted by his barium-striped dilatation bag was sufficient to dilate the cardiac end in achalasia. In one female patient ½ lb. pressure was sufficient. The movement of respiration is transmitted to the barium column, but no peristalsis was seen.

Dr. Campbell Golding of the Middlesex Hospital X-ray Department observed that the inhalation of octyl nitrite diminished appreciably the height of the column of barium necessary to cause a trickle of barium to flow into the stomach. Amyl nitrite upset patients to an alarming extent.

Brown Kelly stated that in achalasia patients when the tube of the œsophagoscope reached the hiatus the orifice closed firmly and relaxed when the tube was withdrawn to about 3 cm.

Dr. Wilhelmina Shaw Dunn divided both vagi nerves in cats, then fed them with barium milk. The X-ray showed a dilatation of the œsophagus without relaxation of the cardiac end. When the œsophagus was full of barium the cat vomited some of the barium. As expected, division of the vagus nerve in a few patients has aggravated the achalasia. Gilbert, Dey and Rall stimulated the vagi of cats and observed the contraction of the œsophagus with drawing upwards of the cardia through the hiatus. Hofer and Spiegel divided all the sympathetic nerve fibres to the œsophagus which could be found and observed that there was no change in the act of swallowing and that the sympathetic nerves were not antagonistic to the vagus. A patient who had had both stellate ganglia of the cervical sympathetic excised for vertigo was watched swallowing barium and no change in the act occurred.

There is sufficient evidence to assume that the cardiac end of the œsophagus remains closed at the hiatal level except during the passage of food. The cardiac end is closed by the contraction of the muscular tube reinforced by the action of the diaphragm similar to the closure of the larynx. The orifice of the larynx is closed by contraction of its muscles and it is then drawn up behind the base of the tongue.

The treatment of achalasia by dilatation through the œsophagoscope has been successful in early cases, when the hiatus is easily seen. The œsophagus should be washed out by large draughts of water or a weak solution of bicarbonate of soda morning and evening. At least half a pint of water should be taken after each meal. If a Hurst's mercury bougie is used the patient should be watched with the X-ray screen to see that the bougie enters the stomach.

The result of treatment is difficult to assess and patients may have no symptoms for long periods. For example 3 cases of achalasia were seen with complete dysphagia after swallowing a cherry stone, a plum stone and a large bolus of meat respectively. The fruit stones acted as ball valves and after removal the patients could swallow normally. The cardiac end was dilated but they did not return for treatment. The majority of cases of achalasia show a steady increase in the dilatation of the œsophagus seen by X-ray photographs in spite of treatment.

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Mr. St. George B. Delisle Gray said he had listened with the greatest interest to these two excellent papers for he himself had suffered from achalasia of the cardia or cardiospasm since he was 29 years old. He is now 57. Personally he thought from his own sensations that it was a true spasm.

The first attack came on when he was drinking iced wine in Portugal. He felt the mouthful stick retrosternally, there was intense colic of the œsophagus for several seconds, the wine regurgitated into his mouth and then was swallowed quite naturally. He thought it was an œsophagual pouch, but was advised by Bizarro (a Portuguese surgeon with the F.R.C.S.Eng.) that it was a cardiospasm. On his return to England the condition got steadily worse; he could not drink hot or cold fluids and used to take everything lukewarm. He had to sleep well propped up as otherwise œsophageal contents trickled over into his trachea and he used to wake up coughing. Since the onset of the cardiospasm he has never vomited stomach contents except recently after dilatation. Several years ago he had an acute attack of pain, vomited up his breakfast and felt extremely ill. The condition was then confirmed by X-ray. He felt very much better after washing out his œsophagus with water. At times during the night he would wake up with acute retrosternal pain of a griping character. This was often relieved by leaning over the bed and emptying the œsophagus into the chamber. He noticed when he did this he brought up small solid chunks of food. If this did not relieve the pain he would get up and drink some water and this by dilating the œsophagus relieved the spasm; he would of course have to empty the œsophagus again.

In spite of this complaint he has lived a very active life and served throughout the War afloat on very active service. While in his ship at Sydney he had an acute attack of spasm. On his return to the U.K. Professor Grey Turner advised him to try a Hurst's Tube (No. 30) which he did, passing it three times a day for five minutes at a time. This greatly relieved his symptoms, and he put on 3 stone in weight in a very short time. For some time he has not been passing the tube as the one he has has become cracked and he did not relish the idea of the tube breaking and getting a stomach full of mercury. It is apparently impossible to get a new one. The condition has since got worse.

On swallowing food it can be felt to stick half-way down the œsophagus, and it is forced on by drinking copious draughts of water, which act similarly to flushing the W.C., when everything gets washed on. There is a sensation that the œsophagus is going to burst, suddenly the cardia relaxes and the food can be heard from the other side of the room passing into the stomach. It is important to drink *cold* water because the sensation of cold in the epigastrium when the cold water reaches the stomach indicates that all the food has passed through. Standing up makes swallowing easier. On passing the tube resistance is felt at the level of the cricoid cartilage. The tube suddenly passes on and is held up again for some seconds (it may be over a minute) at the cardiac orifice. This suddenly gives way and the tube passes into the stomach. After it has been in five minutes it is withdrawn and it can be felt to be gripped by the sphincter. This makes him believe that it is a true spasm and not an achalasia.

[*February* 1, 1950]

A film on **Control of Infection in Surgical Dressings** was shown by Dr. L. COLEBROOK.

The following Specimens were shown:

(1) **Leiomyosarcoma of Œsophagus.** (2) **Stricture of Small Intestine after Relief of Strangulated Hernia.**—Mr. FRANK FORTY.

Long-standing Simple Ulceration of the Cæcum Causing Chronic Intestinal Obstruction.—Mr. A. DICKSON WRIGHT.

Intramural Diverticulitis of the Cæcum.—Mr. JOHN HOSFORD.

(1) **Reticulum-cell Sarcoma of the Duodeno-Jejunal Junction, Treated by Resection of the Third and Fourth Portions of the Duodenum and the First Part of the Jejunum.** (2) **Extensive Carcinoma of the Rectum associated with Recto-Vaginal Fistula and with a Three Months' Pregnancy, treated by Cæsarean Hysterectomy by Wertheim's Method, associated with Synchronous Combined Abdomino-Perineal Resection of the Rectum.** (3) **Retroperitoneal Ganglioneuroma.**—Mr. MICHAEL OLDFIELD.

Suprarenal Tumour.—Mr. E. C. B. BUTLER.

(1) **A Unilateral Polycystic Kidney.** (2) **Pyonephrosis in One Half of a Double Kidney.** (3) **Infected Hydronephrosis in a Supernumerary Kidney.**—Miss A. H. BAKER.

(1) **Porta-Caval Anastomosis (in Continuity).** (2) **Retroperitoneal Portal to Systemic Collateral Anastomotic Channels.**—Mr. ALAN HUNT.

Two Large Epidermoid Cysts Following a Full-Thickness Skin Repair of a Hernia.—Mr. M. R. EWING.

An Unusual Carcinoma of the Thyroid.—Mr. GUY BLACKBURN.

Hæmangioma of the Spleen.—Mr. RODNEY SMITH.

Section of Epidemiology and State Medicine

President—W. H. BRADLEY, D.M., M.R.C.P.

[*December* 16, 1949]

DISCUSSION ON HOSPITAL CONSTRUCTION IN THE LIGHT OF CROSS-INFECTION

Dr. A. G. Watkins: The facts on which this paper are based are largely taken from the recent enquiry, made at the instigation of the British Pædiatric Association (Allison *et al.*, 1946; Watkins and Lewis-Faning, 1949), to try to ascertain the exact incidence of cross-infection in children's wards in hospital. The following definition of cross-infection was used namely: "To denote any infection acquired by a patient in the hospital environment. Clinically it is an infection arising during the course of another illness from which the patient was originally admitted to hospital, and may attack the respiratory tract, gastro-intestinal tract, wound, scar or mucous membrane, or be manifest as one of the specific fevers." The enquiry covered children in 26 wards in 14 hospitals in Great Britain and the net finding was that of just under 10,000 admissions in 1947 there was an incidence of cross-infection amounting to 7% of all admissions. The wards were in charge of consultant pædiatricians and in the main were located in teaching hospitals. This should therefore imply that 7% is a minimal figure for the country as a whole.

The source of infection is usually that of an infected individual admitted to the ward as a patient or an infected attendant. The severity of infection will depend on the extent of the dose passed on, the virulence of the organism and the condition and age of the host receiving it.

The methods of spread are mainly by droplet infection and by direct contamination by handling infected persons or material. A sneeze is a common way by which droplet infection is conveyed to the air in a ward and so infecting the dust. This contaminated dust and air convey the organisms or virus and their passage is increased by movement such as during the process of ward dusting and bed making. Contamination by handling can readily occur when changing napkins, dressing wounds, or if the attendant's skin is harbouring an infection such as a boil or septic finger.

The problem is then, firstly, to prevent the infected persons from contaminating the air and dust and secondly to prevent the air and dust conveying the infection. In the prevention of the accumulation of dust the architect can be of great help. We have known for years that hospitals should never have corners and all nooks and crannies should be avoided. That is of vital importance, but, in addition, we have learnt and are still learning other techniques to reduce dust. Wet-sweeping of ward floors so that dust is collected in lumps and not dispersed in fine particles is of value and oiling of the floors with spindle or white oil helps considerably although not too popular with matrons. Blankets may be oiled so that dust from them during bed making is reduced but this will require special laundry facilities. There is some evidence that washing baby's woollies in the ward by the nursing staff, which is done to avoid shrinkage by the laundry, may not completely eradicate infection.

Considerable advances are being made in air purification and hygiene (1948) but we have not adopted air-conditioning widely in this country. On a visit to a Children's Hospital in New York it was disastrous to find that the ward had to be closed while the air-conditioning plant was being repaired and that as this was during the very hot weather it was quite impossible to open the ward at all.

Disinfection of the air by aerosols is another method of which we have not a great deal of experience here. The practical difficulty is that the substance to be sprayed may be more irritant to the patient than to the organism and aerosols are best used in air-conditioned rooms.

Ultraviolet-ray screens seem to be valuable and are used quite extensively in the United States and Canada. Their use may avoid infection by way of a swinging door which tends to draw air in from a contaminated corridor. They are expensive to erect but reasonably cheap to maintain.

There is no doubt that good cross-ventilation is one of the most important preventive measures we have to keep air from carrying infection. Plenty of open windows with good balcony space are an excellent insurance against cross-infection. It has been shown that ordinary sunlight has some germicidal effect on the dust in the ward.

If a patient has an infection which is liable to be spread it is obvious that he should be isolated from the rest of the ward, and the habit has grown of recent years of dividing children's wards into cubicles to allow individual isolation. In order to be successful cubicles must imply full barrier nursing and each cubicle must be self-contained with the necessary facilities for washing and for a nurse to keep and change her gown and masks. Cubicles should be erected so that they go up to the ceiling. An eight to ten foot barrier is of little use for several reasons. Firstly, a tall nurse can spray her droplets over the top. Secondly, a child standing in his cot is not always averse to spitting over the top or at least throwing toys over the top. Lastly, it is obvious that air contaminated in one cubicle can pass readily to another unless completely shut out. The only time that a cubicle not reaching the ceiling is at all justifiable is if this is the only means for its ventilation. There is one ever-present danger of cubicles. That is that the nursing staff must not think that because a child is secluded in a cell that the ordinary barrier precautions can be relaxed.

Architects can be of great assistance in the designing of these cubicles and above all they can help to ensure that ward units are not too big. By reducing the number of children into small units nursing is better and easier and cross-infection lessened.

Perhaps the most important aspect of the prevention of cross-infection is in the nurses and their training. By this is meant not only the instructions to wear masks and gowns but also training by special education, special lectures and demonstrations so that the nurse can really understand why these seemingly finicky regulations are essential.

There is one nursing danger which seems to be difficult to solve and that is the usual shortage of nurses during night duty. So often one finds that at night one or two nurses are expected to deal with the same number of babies as six or more nurses do during the day; no wonder that minor details of barrier nursing and general precautions tend to get neglected.

Masks should be worn by all who come in contact with small babies—by the doctor no less than the nurse. The mask, however, must be effective and must contain an impermeable layer. It is uncomfortable to wear, particularly when talking to students, but there is no question as to its value, so it should be used, but to be effective it must be used properly.

Acute specific fevers occur by no means uncommonly in a children's ward, and the enquiry referred to revealed that many children are admitted to the wards during an incubation period. In addition to this, children with sore throats or in contact with throat infection are taken in. Careful history taking and examination prior to admission are therefore essential preventive measures. This examination must, however, be done by a senior member of the staff. It is too responsible and too difficult a task to be left to a newly qualified house physician. Provision must be made in the way of a special well-lighted room in which to interview the parents and to examine the child.

At this stage Charts (not reproduced) were shown illustrating the paths by which infection travels; the dangers of ward sweeping and dressing times; the relative incidence of the various types of cross-infection; the increased length of stay in hospital occasioned as the result of cross-infection; and deaths attributed to cross-infection.

The prevention of cross-infection is a threefold problem. Firstly, the medical problem: hospital admissions should be examined carefully to exclude infection; children and especially babies must be protected against infection. Secondly, the help of the architect should be enlisted to design wards of small units, well ventilated and allowing of complete barrier nursing; and lastly it is on the training of the nursing staff that we must rely for the prevention of cross-infection.

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Dr. Thomas Bedford: There can be no doubt that infective material can be transmitted from one person to another *via* the air, but there seems to be no clear indication as to whether, in ordinary buildings, direct infection or airborne infection is the greater risk. In densely occupied rooms the risk of droplet infection will clearly be greater than in sparsely populated ones, but unless the ventilation varies in proportion to the number of occupants the concentration of airborne organisms will also tend to be greater with the denser occupation.

In *hospital wards*, where patients are in bed, it can be assumed that the chances of direct infection will be less than in, say, a factory or an office, and that in hospitals, therefore, aerial infection will be relatively more important. There is evidence that cross-infection in hospitals has been spread by the aerial route.

Much can be done to reduce the numbers of bacteria in the air by using either ultra-violet lamps or one or other of various disinfectant vapours or mists. These methods of air sterilization, properly applied, can be very effective against unprotected, single organisms, but they are less effective against dust-borne organisms. For ordinary wards, good ventilation, coupled with the efficient application of dust-suppressive measures, should do much to reduce the risks of cross-infection. It is true that Dr. Watkins and Dr. Lewis-Faning have recently reported that they could detect no significant association between ventilation and cross-infection, but this negative result leaves me unconvinced. The classification was made on the basis of replies to a questionnaire. Somebody at each of 14 hospitals was asked to give information concerning the quality of the ventilation in wards or cubicles, but there is no indication of the criteria used, or that any measurements were made.

Provision of ventilation.—Whether hospital wards are to be ventilated by natural or by mechanical means, a decision on the amount of fresh air that is to be supplied should be reached in the planning stage. Clearly, if the building is to be ventilated mechanically, the engineer must know what air supply is required before he can design his air ducts and decide on the sizes of fans. Even one with much experience of ventilation will be unable to say with precision what amount of ventilation will be obtained with any arrangement of open windows, but he can probably make a fair guess. Nevertheless, even with natural ventilation a decision must be made about the amount of ventilation to be provided during winter, for the heating engineer must make proper allowance for this in his calculations of heat requirements. If inadequate allowance is made ventilation must be restricted or the wards will be cold.

In the 1937 Report of the Departmental Committee on the Cost of Hospitals and other Public Buildings some guidance on this point is given to engineers. It is suggested that when ordinary convective methods of heating are used allowance should be made for 3 air changes per hour, and that when radiant heating is used this amount may be reduced to some extent. By the standards for ordinary buildings these suggestions allow for good ventilation.

A ventilation rate of 3 air changes per hour does *not* mean that the air within the room is completely renewed three times each hour. Instead, it means that the volume of air entering and leaving the room in one hour is three times the volume of the room. As the air enters the room it mixes to greater or less extent with the air already in the room, so that if any polluting agent is present in the room atmosphere it is gradually diluted by the ventilating air. If mixing is perfect, after the time taken for one air change—twenty minutes in our example—the concentration of the polluting material is still 37% of the original value.

The other basis on which ventilation calculations are made is that of the fresh air supply required for each person. In ordinary practice a fresh air supply of 1,000 or 1,200 cubic feet per person per hour represents good ventilation in cold weather. Now in a factory, where the cubic space available for each person may be only 400 cubic feet, 3 air changes per hour would give 1,200 cubic feet of fresh air per hour for each person. On the other hand, in a hospital ward, where the space allowance is probably 1,000 to 1,500 cu. ft. per patient, 3 air changes per hour represent 3,000 to 4,500 cubic feet of fresh air per hour per person. This seems to be a very good figure, judged by ordinary ventilation requirements, and it makes a considerable demand on a heating system, yet it may not be good enough to be effective in preventing cross-infection.

If the atmospheric contaminant which has to be removed by the ventilating air is being steadily emitted at a more or less constant rate which is proportional to the number of occupants—as, for example, the carbon dioxide in expired air—then the ventilation standard should be in terms of the amount of fresh air required per person, irrespective of the space allowance for each person. Such a standard might be desirable from the standpoint of cross-infection if the infective material were being disseminated more or less constantly by each occupant.

If, on the other hand, there is, perhaps, only one patient in a ward, who may occasionally eject highly infective material, a ventilation rate in terms of the number of air changes per hour is the standard which should be adopted—and the standard may need to be high.

With 3 air changes per hour, twenty minutes after the sudden introduction of some atmospheric contaminant the concentration of that contaminant is still 37% of the original value, if the contaminant is removed only by the ventilating air. After the same interval of time the residual concentration with 6 air changes per hour is only 14%, and with 10 air changes per hour 4%. These calculations make no allowance for the rate at which bacteria-laden particles will settle out from the air. When such allowance is made the contrast is less striking. It is probably reasonable to assume the rate of removal of particles by sedimentation to be about that which would be achieved by a ventilation rate of 4 air changes per hour. If we accept that figure, with an actual ventilation rate of 3 air changes per hour, ventilation and sedimentation together would remove bacteria-laden particles at a rate corresponding to 7 air changes per hour, and with ventilation at 6 air changes per hour the removal rate would be equivalent to 10 air changes per hour. With these removal rates the bacterial concentrations five, ten and twenty minutes after the dispersion of the organisms would be 56, 31 and 10% of the original concentrations with the ventilation rate of 3 air changes per hour, and 43, 19 and 3½% with ventilation at 6 air changes per hour.

It may be thought that the higher ventilation rate is desirable, but, if so, it should be allowed for when the heating installation is planned. I understand that it is recommended that heating arrangements should provide for the maintenance of a temperature up to 30° F. in excess of the outside temperature. Thus, except on relatively few days, when the outside temperature is below 35° F., it should be possible to maintain a temperature of 65° F. in the wards. To me this seems a reasonable temperature. Overheating is undesirable, but the wards should be adequately warmed. A 30° F. excess above the outside temperature will only be possible, however, if the ventilation rate is limited to that for which the engineer has made allowance—generally 3 air changes per hour. Increased ventilation in winter will be got at the expense of lower temperatures.

Some systems of heating set up steep temperature gradients so that the air around the head is several degrees warmer than that near the floor. Such a condition gives rise to complaints of cold feet and of stuffiness in the head. Similarly, a system of radiant heating which exposes the heads of the occupants to an undue amount of radiant heat is undesirable. Heating by steam radiators, especially when high-pressure steam is used, sets up more marked gradients than do hot-water radiators. In many buildings radiant heating by means of low-temperature ceiling panels has been used with much success, but ceiling panels should not be used in low ceilings unless their temperatures are really low. We are working at present on this problem, but it is too early to give precise guidance as to the maximum desirable temperatures of overhead panels.

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Endemic Hepatitis Among U.S. Troops in Post-War Germany

By JOHN R. PAUL, M.A., M.D.

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THE subject of Endemic Hepatitis may not be very appealing because with the war well behind us, many might like to say, "Allow us to forget about hepatitis, particularly military hepatitis". But I would point out that British investigators[1] are prominent among those who have dragged this disease into the open and we should get on with it.

We in the United States have been concerned with the fact that the incidence of hepatitis among U.S. troops within the American zone in Germany has not only continued to be high but has even been rising until it is to-day comparable to that noted in certain combat areas during the war, with an average of 14 cases per 1,000 per annum. Hepatitis has been a scourge to our military forces since 1942. During World

[1] I refer here to the work of W. N. Pickles, G. M. Findlay, F. O. MacCallum, W. H. Bradley A. M. McFarlan, and others.

War II it "fell like a bombshell" on the U.S. Army, which was hardly prepared for it. The first "bombshell" was the outbreak of homologous serum jaundice, which will hereafter be referred to as serum hepatitis (SH), for which inoculations of yellow fever vaccine were found to be responsible at that time. Then in 1943 and again in 1944 came large outbreaks of infective hepatitis (IH) in the Mediterranean area, in which British forces were also involved. From experimental work on the disease, which emerged from several laboratories at that time (and will not be quoted here in detail), it became apparent that at least two viruses were concerned: one responsible for infective (or infectious) hepatitis representing the naturally occurring disease; and the other responsible for serum hepatitis, apparently an artificial disease. The two diseases give approximately the same clinical picture and often appear intermingled at the same time and place. With infectious hepatitis (IH) there is a relatively short incubation period (fifteen to thirty days); contact cases are common, and the virus is found both in the fæces and blood during the acute stage and can be transmitted orally. With serum hepatitis (SH) the incubation period is much longer (fifty to one hundred and twenty days); contact cases are uncommon; virus has been detected only in the *blood*, during the incubation period as well as the acute stage, and transmission has so far been accomplished only through parenteral infection. There is no demonstrable cross immunity between the two viruses, and attempts to transform one into the other have, I believe, been entirely unsuccessful. Both diseases can be transmitted by needles or other instruments. While the *origin* of infectious hepatitis may not be particularly clear, that of serum hepatitis is completely shrouded in mystery. Whatever its origin may be, however, it obviously did not start in a syringe. The syringe merely seems to be an effective, mechanical vector.

From an epidemiological standpoint, infectious hepatitis appears to be world-wide in distribution. There are, however, certain geographical areas where rates in immigrant troops have consistently been high. Thus China, the South Pacific, the eastern half of the Mediterranean area, Italy, and also southern Germany are places where the hepatitis rates were particularly high in U.S. troops during and following World War II. This high "icterogenic capacity" characteristic of some geographical areas may not necessarily be reflected by the local civilian hepatitis rates, for the endemic disease in civilians is often poorly reported.

From a seasonal standpoint, the autumnal rise in the morbidity rate is a characteristic feature of infectious hepatitis. During World War II the hepatitis rates in U.S. troops in North Africa and Italy rose sharply in 1943 and 1944, in October. This same autumnal rise has been characteristic of the civilian disease in Denmark and Sweden. It may be of some significance, therefore, that seasonal fluctuations of hepatitis in U.S. troops in post-war Germany have not shown this sharp autumnal peak but instead an ill-defined double peak—occurring in the autumn and early winter respectively. Furthermore, this is contrary to the single autumnal peak seen among British troops in their zone in post-war Germany. The question arises, therefore, as to whether cases of serum hepatitis may not be frequently intermingled with those of infectious hepatitis in the U.S. troops to produce this different seasonal picture. Actually the existence of serum hepatitis has been proven experimentally to be present among these military cases.

As for seasonal fluctuations of serum hepatitis, it might seem that there is no particular reason for such to exist. But there are some data on this, available from Ruge's studies in the 1920s in Germany, on "salvarsan jaundice". His clinical material largely came from the German Navy and he found that the highest incidence of the disease in patients, who were receiving antisyphilitic therapy, occurred in January. One speculates as to whether or not his January peak may not have been related temporarily to the high autumnal peak of infectious hepatitis indicating a two-month lag between the two peaks, which is a period of time perhaps comparable to

the long incubation period of serum hepatitis. If this explanation were correct, one would assume that a closer relationship between infectious hepatitis and serum hepatitis exists than has heretofore been thought to be the case. Thus the theory that serum hepatitis virus may conceivably be a variant or a relative of infectious hepatitis virus could be based on the speculation that the two diseases seem to occur simultaneously or consecutively in time and place.

As to other details with regard to hepatitis among U.S. troops in the American zone of Germany, the disease has occurred most frequently in young individuals who have been in the area a relatively short time, with cases developing around the ninth to the tenth month of service. The cases have been quite sporadic in distribution. The incidence has been about the same among coloured as in white troops and has borne no special relation to service or rank.

Investigations have been made to try to determine whether the immunization of troops or the administration of penicillin could have contributed to the spread. There is some evidence that men with hepatitis have had a greater penicillin history than others but the data are not particularly convincing.

Summary

Evidence has been presented to indicate that infectious hepatitis has been prevalent and endemic in Germany for many years, particularly in Bavaria. Therefore it is not surprising that this disease should have been common in the U.S. Army of Occupation during the post-war years, 1946–50. It has been our suspicion that many, if not the majority of, U.S. soldiers who acquire hepatitis in Germany, do so as a result of direct personal contact with German households. But coupled with the natural disease, it would also seem probable that the infection has been maintained in this military population by the artificial transmission of both infectious hepatitis as well as serum hepatitis, via syringes and needles. The evidence for this is largely circumstantial but it has been proven experimentally in one instance, and there is considerable ground for suspicion that it is a frequent occurrence. Thus the seasonal curve of hepatitis among U.S. troops has more or less consistently shown some deviations from the usual autumnal rise and early winter decline of infectious hepatitis cases as seen in civilian populations, and among troops in combat previously and elsewhere. These deviations are compatible with the idea that some or even many of the winter cases are examples of serum hepatitis. If this conclusion is correct, it lends weight to the idea that serum hepatitis and infectious hepatitis are more closely related to one another than previous experimental work has perhaps indicated.

I have to thank our Military Authorities for permission to publish.

Section of Obstetrics and Gynæcology

President—LESLIE WILLIAMS, M.D., M.S., F.R.C.S., F.R.C.O.G.

[*January* 20, 1950]

Adeno-fibroma of the Fallopian Tube Undergoing Malignant Change.—DOUGLAS MACLEOD, M.S.

This term is suggested for an unusual tumour of the fallopian tube which histologically was seen to consist of large masses of epithelial cells, some of which appeared to line branching clefts. These clefts were surrounded by a network of stroma cells. The epithelial formations and the stroma cells both showed malignant characteristics. The tumour was pedunculated, roughly oval in shape and lying in the lumen of the tube; it measured 6 cm. by 3·5 cm.

The pedicle was found histologically to be invaded by malignant tissue as far as its base.

The tumour occurred in a woman aged 55 who had had a radium induction of the menopause six years previously ; her only symptom was pain over the site of the tumour.

The patient died 14 months after operation from extensive sarcomatous deposits on the peritoneum.

Congenital Diverticulum of the Uterus Revealed by Uterosalpingogram.—DOUGLAS MACLEOD, M.S.

A case of congenital diverticulum of the uterus in which a recent pregnancy had occurred was demonstrated by uterosalpingogram. The first, taken nine days after the miscarriage, showed a circular diverticulum, 3·25 cm. in diameter, springing from the uterine fundus near the right cornu. In the second salpingogram, taken nine months later, the diverticulum had reduced in size to that of a pea. The patient had had three, previous, normal labours.

Subtotal Vaginal Clamp-Hysterectomy for Chronic Inversion of the Uterus.—I. BIERER, M.D.

Mrs. A. P., aged 57, was admitted on February 9, 1946, to Bethnal Green Hospital as an emergency case. She had had three children, no miscarriages. Regular periods; but for the last twelve years intervals of from three to six months between them. For the last six months she had felt something hanging down from her vagina and had recently had a copious vaginal discharge and heavy uterine bleeding. For the last twelve hours she had had severe hypogastric pains and had fainted on the day of her admission to hospital.

On admission her temperature was 97·6°, pulse 76, B.P. 130/90, her normal B.P. being 220/140. She was suffering from a moderate degree of shock. The patient had always been a very healthy woman, her weight being 17 st. 7 lb., and her height 5 ft. 5 in.

The gynæcological examination of this patient revealed a mushroom-like tumour, the size of a Jaffa orange, protruding through the vagina, which was rather tender, congested, and unhealthy in appearance with a fibroid on the top of the mass. The lower abdomen was tender too. The patient was prepared for the theatre, and an examination under anæsthesia was performed. A metal catheter was introduced into the bladder and a finger into the rectum. They met readily without interference by the uterine body, therefore the diagnosis chronic inversion of the uterus was made.

Chronic inversion of the uterus is rare ; complete inversion is rarer still. In the majority of cases it is puerperal in origin, commencing as an acute inversion. In a minority of cases it is due to the presence of a tumour, a submucous fibroid, a sarcoma, or a carcinoma.

The most suitable method of treatment in these usually infected cases seems to be vaginal hysterectomy with drainage. The maximum drainage is achieved by clamp-hysterectomy. In this case a subtotal vaginal clamp-hysterectomy was performed.

Pryor-Kennedy's clamps were applied to each side of the protruding mass after a small incision had been made first on the posterior and then on the anterior wall of the inverted uterus.

The body of the uterus was amputated, the widely dilated cervix being left with the four clamps which were finally removed after seventy-two hours. A vaginal plug was inserted for forty-eight hours.

The patient's temperature did not exceed 100·2° for a few days. She made a smooth recovery and was discharged on March 12, 1946. She was last seen on February 28, 1949. The cervix was closed and there were no visible marks of the operations. The patient felt well.

Vaginal clamp-hysterectomy provides excellent drainage, the powerful Pryor-Kennedy's clamps will prevent retraction of vessels and there are no ligatures to slip. There is no danger of pulmonary embolus (Kennedy and Campbell, 1944), the operation is simple and can be performed quickly.

REFERENCE

KENNEDY, J. W., and CAMPBELL, A. D. (1944) Vaginal Hysterectomy. Philadelphia.

Dicephalic Monster.—D. W. JAMES, M.B.

Specimen was shown with radiograph, autopsy report and historical review. The monster weighed 7 lb. and was delivered as a breech, with craniotomy of one after-coming head.

Uterine Irritability as a Cause of Dyspareunia.—EDWARD COPE, M.B.

In 1937 Dickinson described a clinical method by which it was possible in the healthy non-pregnant woman to detect rhythmic uterine contractions. He performed 89 pelvic examinations on 5 women during various phases of the menstrual cycle and found that the uterus was most active for three or four days before and three or four days after ovulation. During this period the uterine contractions occurred at intervals of from two to ten minutes. Following this the uterus was in a state of relative quiescence, but again became active a few days before the onset of menstruation and this activity continued during menstruation.

It is furthermore well known, as a result of work by Malpas, that even in early pregnancy the uterus undergoes regular contractions. This phenomenon was also described by Palmer (*Proc. R. Soc. Med.*, 1950, **43,** 99).

Stallworthy in his Address to the Royal College of Obstetricians and Gynæcologists, states that " previously unsuspected uterine irritability is the most common cause of tubal occlusion "; he further states that " the female genital tract is the most hysterical portion of a woman's anatomy. . . . It manifests its independent rebellious spirit in a multitude of ways; the so-called functional or intrinsic dysmenorrhœas, vaginal spasm and vaginismus, to mention but some of the common manifestations of this disharmony ".

The following is a short account of 3 cases in which this disharmony is manifested by a uterine irritability of such a degree as to cause severe dyspareunia.

The first case was the wife of a publican. A nullipara aged 50. Menopause twelve years ago ; no post-menopausal bleeding or discharge.

She complained of severe mid-line lower abdominal colicky pain which occurred only after orgasm, and lasted half an hour, but that as orgasm was the usual sequel of intercourse, and as her pain was severe, her life was being made miserable.

The only significant incident in her previous medical history was that eleven years ago she had had a dilatation and curettage for an intra-uterine polypus. The records of this operation were not available. She thought that the pain of which she complained dated back to this operation, but it was only in the past two to three years that it had become really severe.

She was a healthy-looking, well-built woman, and apart from a blood pressure of 180/100, nothing abnormal was found on general medical examination.

Pelvic examination revealed that she had a mobile retroverted uterus and that the left ovary was cystic and enlarged to the size of a pullet's egg. Nothing else abnormal was felt. A diagnosis was made of post-coital pain due to strong uterine contractions.

In view of the severity of her symptoms it was decided to remove her uterus. At operation it was found that the uterus was slightly enlarged, and that there was a small subserous fibroid in the posterior wall. The ovarian cyst, which had been palpated, proved to be a small serous cyst of the left ovary. Total hysterectomy with bilateral salpingo-oophorectomy was performed. Examination of the uterine cavity revealed a friable irregular polypoid mass $5 \times 3 \times 1$ cm. in size which appeared to invade the myometrium and which on section proved to be an adenocarcinoma of the body of the uterus. The patient made an uneventful recovery and intercourse is now satisfactory.

It seems probable that this patient had an irritable uterus, and that the increased tension in the uterus due to the intracavitary tumour increased the strength of the uterine contractions to such an extent that they caused severe pain. This is in accord with the work on uterine tension by Reynolds and by Knaus, who found that an increase in the volume of the uterine cavity by only 3 – 4 c.c., raised the uterine tension sufficiently to increase the strength of the uterine contractions.

The second case was a nullipara aged 19 who complained of similar pain following intercourse. Examination revealed nothing abnormal. A diagnosis of uterine irritability was made and pethidine 100 mg. was prescribed, to be taken before intercourse. This relieved her pain and she became pregnant during the next menstrual cycle.

The third patient was a para-1, aged 34, who complained that for the past five months she had had colicky hypogastric pain on intercourse. She had also had menorrhagia since the birth of her baby two and a half years ago. Examination revealed nothing abnormal but in virtue of her symptoms a diagnosis of uterine irritability associated with an intra-uterine polyp was made.

Dilatation and curettage was performed and an endometrial polypus was removed.

Dickinson states that in women: "The much exploited (uterine) rhythms in orgasm fall into the class of erotic fiction until evidence by trained observers is submitted." Although the uterine contractions were not palpated in any of these cases, their histories and the results of treatment indicate that their symptoms were due to uterine irritability.

In 2 of these patients there is an additional factor which would be likely to increase the strength of uterine contractions stimulated by intercourse. If it is a fact that intercourse may in some women stimulate uterine contractions of such a degree as to cause pain, then the implications are considerable in infertility, abortion, particularly at the so-called critical period when the progesterone level may be reduced, and in the diagnosis of intra-uterine tumours.

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The following specimens were also shown:

Vesicular Mole with Vaginal Metastasis.—Dr. R. MAGNUS HAINES.

Chorionepithelioma of the Ovary.—Dr. A. PEARSON.

Labour Complicated by Pheochromocytoma—Sudden Death.—Dr. C. T. F. EALAND.

Two Cases of Struma Ovarii.—Dr. P. HUGHESDON.

Dicephalic Monster.—Dr. N. PERKY.

[*February* 17, 1950]

DISCUSSION ON RESUSCITATION OF THE NEWBORN

Dr. J. Edgar Morison (Belfast) : The pathologist must first try to decide what proportion of infants die because resuscitation procedures fail. When death is due to congenital anomalies, to birth trauma, to infection and to various other conditions it may be preventable, but scarcely by procedures which are now to be reviewed. These conditions all produce recognizable and often highly distinctive structural changes but many other fœtuses and infants do not show these lesions.

The absence of these lesions and the presence of certain other less specific changes suggest that these children die only because they are exposed to conditions in their intra-uterine or extra-uterine environment which themselves directly produce fatal anoxia. Such an extrinsic or environmental anoxia may be due to some insufficiency of placental transfer, a misfortune of the mechanics of labour, some disaster to the cord, or an environmental accident, such as the aspiration of excessive amounts of amniotic sac debris or mucus into the air passages. This anoxia always favours birth trauma and infection, but by itself it may be responsible for death. This may be recognized by grouping together for further analysis all deaths which are due to anoxia alone. If these children are born alive, that is with pulsating umbilical vessels, their failure to live is a failure of resuscitation avoidable or unavoidable.

As thus defined the importance of asphyxiation in intra-uterine and extra-uterine life can be seen from Table I derived from an analysis of 1,074 cases all of viable maturity from our in-patient hospital services (in Belfast) recently studied with complete routine histology from every organ of the body.

The causes of anoxia, or at least its immediately precipitating causes, can sometimes be discovered by a review of obstetrical details and autopsy observations. In Table II intra-

TABLE I—CAUSES OF FOETAL AND NEONATAL DEATH (PER CENT)

	Ante-partum	Intra-partum	Neonatal Days 0–3	Neonatal Days 4–31
Congenital abnormality	7	10	11	16
Trauma	–	12	17	4
Infection (all types) ..	6	16	19	55
Anoxia (extrinsic) ..	24	52	43	>1
Miscellaneous	10	6	9	11
Not ascertained ..	53	4	1	13
Total cases	169	266	366	273

TABLE II.— INTRA-PARTUM STILLBIRTHS (266) CAUSES OF ASPHYXIA (PER CENT)

Accidents to cord	16
Hæmorrhage: Placenta praevia ..	4
Hæmorrhage: Cause obscure ..	16
Complications of mechanics of labour	21
Miscellaneous	4
Not ascertained	39

partum stillbirths are analysed. Often this is only to introduce one stage further back an unknown cause, often it is only to provoke endless discussion on the right or wrong management of a case. Especially as term approaches the oxygen requirements of the fœtus are dangerously close to the maximum the function of the placenta can provide. The functional reserve of the placenta must vary considerably from fœtus to fœtus, but it is often dangerously small for a difficult or prolonged labour. Until more is known of how to measure this reserve any comparison of one case with another, or one procedure with another, is incomplete. Only comparisons between large, carefully selected and comparable groups are valid.

When liveborn infants are considered, the basis of the failure to establish respiration is often anoxia due to some such insufficiency commencing in intra-uterine life. It is complicated by various factors concerned with pulmonary respiration and with the establishment of the circulation of extra-uterine life. First there is the maturity of the newborn infant (Table III).

TABLE III.—DEATH: THREE DAYS AND UNDER BY MATURITY (PER CENT)

	Term	2,500–2,000	2,000–1,500	1,500–1,250
Congenital abnormality ..	11	4	10	6
Trauma	26	16	6	6
Infection	21	22	27	3
Anoxia	31	47	49	80
Miscellaneous and unknown	11	11	7	3

The handicaps of the premature infant could be discussed in great detail. Only rarely and in very premature infants do they render extra-uterine life impossible. These handicaps include a simple lung pattern with resultant lack of surface for interchange between air and blood, the paucity of pulmonary blood vessels and their separation from air spaces by groups of cuboidal epithelial cells. Irregular expansion of air spaces is contributed to by the scanty elastic tissue in the immature lung. Other disadvantages include immature respiratory centres, weak muscles of respiration and poorly supported blood vessels which rupture readily and lead to asphyxial hæmorrhages, such as those which sometimes rupture into ventricles of the brain. Other factors which should be considered are concerned with the intra-uterine aspiration of amniotic sac debris. Premature infants especially seem unable to eliminate this material from the respiratory passages, and, in their œdematous lungs, its movement in air currents at least contributes to the formation of hyaline membranes. These in turn produce extensive secondary atelectasis in the hours and days following birth. These factors must all be allowed for in any assessment of the value of resuscitation procedures.

Some asphyxiated fœtuses are born showing the effects of an asphyxia which has existed for only a few minutes before their birth. Usually their resuscitation is an immediate success or failure, though a few may succumb later because they have aspirated vernix debris which may form hyaline membranes or because of infection. In another group intra-uterine asphyxiation has continued longer, metabolites of imperfect tissue metabolism in the fœtus have altered the permeability of capillary walls and fluid has passed into the extravascular space. There is œdema of all loose connective tissues, œdema of the stroma of the lung and perhaps, though it is difficult to demonstrate satisfactorily, œdema of the brain. The fœtus differs from an organism living an independent existence. There, until the capillaries are severely damaged, only limited amounts of fluid may pass from the blood into the tissue spaces. In the fœtus transfer of water and salts across the placenta occurs freely and the relatively large blood volume of the mother may permit much larger amounts of fluid to pass to the

extravascular space of the fœtus with little fœtal hæmoconcentration or disturbance of osmotic pressure. For this and other reasons, and especially in premature infants, intra-uterine anoxia causes œdema fluid to accumulate readily and in large amounts in fœtal tissues. The outcome of resuscitation in these infants is often long in doubt, though sometimes it is their subsequent course which gives more anxiety than their first breath. Amniotic fluid is poorly absorbed from the lungs as air enters after birth and fluid readily re-accumulates in the air spaces, oxygen transfer from blood vessels to tissue cells is impeded and metabolism impaired. Whether any procedure more active than withholding fluid feeds from these infants is possible may be considered. The obstetrician listening to the fœtal heart during labour will also remember that it is not alone the severity of asphyxia, but also its duration which is important.

When an infant is born asphyxiated or heavily anæsthetized and in need of active resuscitation the higher respiratory centres are no longer active. The reception of, and response to, stimuli from skin, from muscle, joints, and from the blood-pressure rise following ligature of the umbilical cord are seriously diminished or absent, and carbon dioxide is present in excess in the blood in these cases. The onset of breathing too often depends on the stimulus of severe oxygen want and the response is an unco-ordinated inspiratory gasp. Progress in resuscitation depends on removing the depression of anoxia or narcosis from the respiratory centres, so that rhythmic breathing, mediated by the controlled activity of all the respiratory centres and by pulmonary reflexes, may occur. As long as the circulation continues any movement of oxygen into the air spaces of the lungs should be of benefit for this purpose. Certain procedures, such as rocking, mouth to mouth respiration or various machines may have certain advantages. A viable infant will, however, probably always gasp without such assistance, and those with prolonged experience have rarely retained that enthusiasm for these procedures which theoretical considerations might seem to justify. They probably increase the risk of infection and unless used with care they may produce a pulmonary interstitial emphysema or injure the liver. The operator is, indeed, always more important than the technique.

After birth much amniotic fluid has usually to be removed from the lungs, and though large amounts can be quickly absorbed by an adequate circulation, a slight downward tilt of the air passages will help, especially to eliminate particulate material. With this as a routine we have only twice found plugs of meconium in the air passages. Much of this had been drawn far beyond the reach of bronchoscopic aspiration in the few minutes these children lived.

The most important impediment to normal respiration is usually some disturbance of oxygen interchange in the lung. The anatomical basis for this may be considered. Fluid is last absorbed from, and first accumulates in the most peripheral parts of the respiratory tree. Within a lobule surface tension and not gravity dictates this distribution. Some degree of primary or secondary atelectasis is almost universal even in full-term infants. This also affects the peripheral portion of the air-space system. Both these disturbances reduce the respiratory surface disproportionately more than the volume of the respiratory tree. This involves a loss of opportunity for respiratory exchange which is disproportionately greater than the diminution of the air-space volume. The functional value of the available air space is therefore disproportionately reduced. It is almost impossible to assess these anatomical findings quantitatively or in terms of function, and assessment of their importance is made even more difficult because they tend to progress rapidly in the period immediately before death. Morbid anatomy urgently needs assistance from physiology. If the blood oxygen content is not to decline rapidly as these conditions progress we may expect the respiration rate, and even the volume breathed per minute by infants so handicapped, to be increased well above normal. However, this will probably only occur if the respiratory centres in the brain are intact. Only functional studies during life can indicate the time of onset, the probable extent, and the progress of these disturbances and thus guide our therapy.

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Electrical Stimulation of the Phrenic Nerve

This is an interim report of a method of artificial respiration applied to newborn babies, which has recently been described by Sarnoff *et al.* (1948*a* and *b*) and Whittenberger *et al.* (1949) for animals and adult human subjects. In a series of papers they have shown that the phrenic nerve may be stimulated by a suitable current through the intact skin, and this will result in contraction of the diaphragm and marked inspiration. With modern electronic equipment a current may be applied which moves the diaphragm in a way which closely mimics normal diaphragmatic contraction.

The principle of causing respiration by stimulating the phrenic nerve is not new. In 1783, in his treatise for the Doctorate of Medicine of the University of Göttingen, C. W. Hufeland described the responses of dogs which had just been drowned to electrostatic

stimulation. He mentions the marked respiratory movements which occurred when the phrenic nerve was stimulated. Ziemssen (1857) applied a Dubois Reymond stimulator (shocking-coil) to the phrenic nerve of a man nearly dead of coal-gas poisoning, with successful results. Sansom (1865), in his book on chloroform anæsthesia, cites three references to successful use of the shocking-coil in cases of collapse under chloroform. Two of the cases show it was used with success in London at that time.

More recently, Israel (1927, 1928) applied the Dubois Reymond stimulator to the phrenic nerve in a series of cases of asphyxia pallida, and was successful in many of them after other more conventional methods of stimulating respiration had failed. He found that it was quite possible to stimulate the phrenic nerve through the intact skin of the newborn baby. He stated in his last paper that there had been no death in the University Hospital of Bonn from primary respiratory failure in the newborn in the six months during which the machine was in use.

The apparatus which I have used was designed by Mr. P. W. Roberts of the Physics Department of St. Mary's Hospital Medical School. It is an electronic device which has an output of negative-going rectangular pulses of 1-2 M/sec. duration, with an interval between the pulses of about 8 M/sec. During a stimulation the successive pulses increase in voltage towards a short plateau. The output impedance of the generator is approximately 1,000 ohms. There are independent controls of the period of stimulation to the period of relaxation, and the frequency of repetition of stimulation is also variable. The voltage which may be applied can be varied through wide limits, but a precise specification of this does not seem desirable until more experience has been gained in this method.

Case report (24.6.49) (Patient of Mr. Leslie Williams').—A primipara was delivered of a male baby at 9.45 p.m., after a difficult instrumental delivery *per vaginam*. The baby was pallid and flaccid on delivery and breathing, when it was established, was irregular and shallow. The air passages were cleared of mucus, lobeline was given into the cord, and oxygen was played on to the face. The infant was left in an oxygen tent and not seen by me until three and a quarter hours after birth, by which time it had twice been pronounced dead and the breathing consisted of single gasps at more than one-minute intervals. The stimulator was used with a large indifferent electrode placed on the back and the active electrode in the region of the phrenic nerve. After three-quarters of an hour of successful stimulation the baby was a good colour and breathing spontaneously. Up to the present time the child appears to be developing quite normally, both mentally and physically, and is being observed by Dr. Reginald Lightwood.

There are obviously many details of this method which are not yet known, and it is impossible to assess whether it should be used routinely for asphyxia in Maternity Departments. A further report will be made when this information is available.

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Dame Louise McIlroy: The most dangerous age in our lives is the first twenty-four hours after birth. During labour more attention should be directed to the condition of the fœtus.

Infant mortality has been much reduced in the present century, but there has been little reduction, however, in fœtal and neonatal mortality.

A high percentage of deaths is due to anoxia or want of oxygen, both among premature infants and at term.

Some infants survive but die within four weeks from pulmonary and cardiac complications.

The term asphyxia is confusing. There are gradations from the milder forms of suffocation, due to obstruction in the air passages, to the severe type with heart failure; both are due to the deprivation of oxygen.

Blue asphyxia or apnœa is caused mainly by obstruction of the upper air passages by fluids, mucus, vernix or blood. This takes place before and during delivery. If respiration is retarded the infant passes into a condition of *white asphyxia* or *shock* owing to failure of the heart or its carotid and aortic accessories.

Apnœa as a rule is of short duration under skilled treatment.

Respiration may be delayed in some cases to ten to fifteen minutes provided the heart action is maintained, otherwise death takes place. In law a child is born dead if the lungs

do not function even though the heart may be beating after birth. Before delivery the fœtal heart may become irregular, rapid, followed by slowing down, and convulsive movements occur, as the fœtus endeavours to obtain more oxygen. Meconium in head presentations indicates paralysis of the anal sphincters.

The causes of asphyxia are very numerous.

During pregnancy many are preventable by efficient antenatal care, and investigation of the health of the mother.

Cephalic version carried out so frequently for restitution of breech positions endangers fœtal life. Spontaneous version takes place in most cases before the 36th week of pregnancy. Premature separation of the placenta is a common cause of fœtal death, and in placenta prævia is difficult to avoid, especially if there is operative interference.

X-rays should be more frequently employed to gain an accurate picture of fœtal conditions. Malpositions of the fœtus can be rectified in some cases by posturing the expectant mother in the late weeks of pregnancy.

During labour there is more danger to the fœtus if the mother is an elderly primigravida, or one who has had numerous children with short spacing in between. Prematurity and post-maturity, disproportion between the fœtal head and maternal pelvis, all contribute to fœtal dangers which may result in damage of the respiratory and circulatory intracranial centres.

Excessive uterine contractions diminish oxygen supply to the fœtus, also cord obstruction by prolapse or torsion cut off oxygen, as it is the only pipe-line of supply to the fœtus.

Narcotics and also anæsthetics, if deep or prolonged, should be given with great care and judgment. For the present nitrous oxide and oxygen seems to be the only safe method for light anæsthesia in the second stage of labour. One of its chief advantages is that it distracts the attention of the patient if self-administered. Giving oxygen to the mother is sometimes of benefit in overcoming fœtal heart distress.

During delivery the most frequent cause of anoxia is precipitate delivery by hurried and forcible efforts by the attendant if labour is prolonged. Forceps are the source of danger if the blades are misapplied to the head, and not relaxed during the intervals between uterine contractions. The result is often intracranial injury.

Extraction should be slow even up to twenty minutes. Forceps are much more easily applied and controlled if the patient is in the cross-bed lithotomy position, the operator remaining seated.

During delivery in every case as soon as the mouth of the child appears from under the perineum it should be wiped out by the finger covered with gauze, and the nose squeezed free of fluid. This prevents many cases of delayed respiration.

Management of the newborn.—As soon as the infant is born it is laid on its right side, and immediately covered by a warm coverlet to prevent loss of heat, as it loses heat by transference from the uterus to the air.

When the cord has ceased to beat and is separated, the infant is carried to its tilted warm cot. Lifting should be by one hand under the shoulders, and one under the buttocks with as little movement as possible. The head is lowered to allow fluid if present to pass out of the mouth with the infant lying on its right side. It is allowed to rest from its delivery, and later cleansed with olive oil and dressed.

No baths are given until the cord has separated—about the fifth day. The late Professor Pembrey of Guy's, on going round our wards in the Obstetrical Unit of the Royal Free Hospital, asked why we were so careful in our treatment of the premature infant by warmth and oiling and yet allowed loss of heat by bathing the ordinary infants. We therefore verified this statement by taking the rectal temperature of 100 newborns before and after the first bath, and there was a loss of 1–2° of heat.

Bathing was discontinued and all infants cleansed with olive oil with good results, and less loss of weight in the first few days after birth.

If fluid collects in the mouth or pharynx of the newborn it should be removed by the soft rubber catheter with a glass mouthpiece and inlet to see the rise of the fluid. A metal instrument may injure the soft tissues of the throat.

Complicated and expensive methods of blowing air into the trachea are as a rule only suitable for hospital practice and in skilled hands. They are not obtainable in domiciliary practice more especially in that of midwives.

If the infant still cannot breathe, or only by spasmodic efforts, oxygen (95%) and carbon dioxide (5%) should be given on a mask supplied by a small cylinder with safety pressure apparatus as devised for me by Siebe Gorman.

Lobeline ½ c.c. (as suggested to me by Professor Raper), when injected into the umbilical vein, acts as a stimulant and gives relief in some cases.

Further research is required by physiologists and pathologists into the cause of intra-uterine activity and asphyxia.

I feel convinced that any forcible method of artificial respiration is dangerous, further than

gentle compression of the chest by hand. If there is circulatory failure, massage of the heart by the hand under the ribs is of benefit.

Mouth to mouth inflation is only mentioned to be condemned. Its only advantage is that it may cause entrance of air into the stomach and so cause pressure on the diaphragm which may stimulate respiration. Sepsis and pneumonia has been the fate of some infants after this method of insufflation.

Resuscitation methods, such as that of Schultze, have caused deaths. Even hanging the infant up by the heels as advised in modern textbooks is dangerous, especially if intracranial injury is present, a condition which is difficult to diagnose.

We can only promote expiration at the best. Inspiration depends on the infant when we clear and stimulate the air passages.

[Part of a film was shown to demonstrate delivery in a normal case.]

Mr. J. B. Blaikley: I do not propose to discuss at any length the baby that is born in a state of moderate anoxæmia, and in whom, following the clearing of the airway, respiration is quickly established, but rather the baby which fails to breathe readily and which becomes limp, and in which the heart begins to fail, the condition usually termed asphyxia pallida. The factors responsible are, in varying degrees, prolonged lack of oxygen, shock, pain-relieving drugs such as morphia. Unless prompt measures are taken some of these babies will die, though admittedly many others will belatedly start to breathe spontaneously.

Mr. Gibberd and I (1935) studied the problem of resuscitation of the newborn in 1933, more particularly because of the difficulty in resuscitating babies delivered rather soon after morphia and scopolamine. I was disappointed in the effects of coramine (nikethamide) and the methods of resuscitation then in use. The logical answer seemed to be to inflate the lungs with oxygen, and the simplest way to do this seemed to be to pass an endotracheal catheter and blow the oxgyen in under pressure.

The apparatus we devised is simple and efficient. It consists of a small Magill's silk web catheter which can be passed into the trachea by touch, or with the help of a small laryngoscope, a 2-litre rubber bag connected to a cylinder of oxygen and CO_2, a T-piece inserted into the rubber tubing between bag and catheter to which is attached a manometer registering cm. of water. The bag being full, steady pressure is made on it with the hand up to 30 or 35 cm. of water. The bag acts both as a reservoir and also as a buffer which prevents any sudden rise of pressure in the lungs, which will rupture alveoli, as would be possible if the cylinder was connected straight to the catheter. The catheter should be size 3 or 4, one which leaves adequate space for the outflow of gas through the glottis. The pressure of gas in the lungs is half that in the bag. I have never had an accident, nor do I know of an accident at Guy's. The occasional accident reported has always been through omitting the bag, and connecting up the oxygen cylinder direct to the catheter.

I have now used this method for seventeen years, and on a number of occasions have found it invaluable. It is, I believe, the most certain way of resuscitating a baby, indeed I cannot recall a failure except where autopsy has shown intracranial hæmorrhage or there has been no sign of life at birth. In the knowledge that I can readily start respiration, I have felt happier about the use of analgesic drugs late in labour, and have therefore used them more freely, with advantage, I believe.

I have, during the years, changed my ideas about the way in which the method works. Autopsies on babies with intracranial hæmorrhage which have been insufflated show very little, or even no, expansion of the lungs, and I believe the improved colour which immediately follows insufflation and indicates relief of the anoxæmia, with the result that the pulse strengthens and spontaneous respiration commences, is due to absorption of oxygen through the mucosa of the trachea and bronchi. I have, however, on many occasions noticed that the passage of the catheter has caused immediate inspiration, apparently in a reflex manner; some of these babies after birth had made one or two inspirations and then apnœa supervened apparently as a result of inspiration of mucus. In such cases I often start by aspirating the contents of the trachea and bronchi through the catheter.

There is still much discussion as to whether oxygen or oxygen and CO_2 (5%) should be used. The general opinion is in favour of the former in view of the fact that there must already be a high CO_2 concentration in the blood, but on the whole I favour the latter. I always think that deeper inspiration results, with presumably greater expansion of the lungs; further I believe that many babies have been subjected to a high CO_2 concentration for many hours—in postmature babies, perhaps for many days—and that the medulla has become accustomed to this, so that a sudden marked fall in concentration is responsible for feeble respiratory movements. If this is so, it is necessary to maintain a high CO_2 level in the blood till respiration is well established.

Lobeline 1/20 or 1/30 grain I find very variable in effect and often it fails to induce inspiration; I have really given up using the drug along with all the others, and rely entirely

on the method of resuscitation I have described. It is very difficult to know whether there are any ill-effects of anoxia on the C.N.S. of the child in very severe and prolonged cases, and in actual fact they are probably very rare. There seems no sense, however, in taking chances and I will conclude by insisting that if a baby is born in asphyxia pallida no time should be lost in clearing the airway, and if the child does not breathe promptly then the lungs should be insufflated. The child's urgent need is for oxygen and the sooner the medulla is "pink" the sooner the respiratory centre will function and the failing circulation recover.

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Dr. B. G. B. Lucas: It is first relevant to review fœtal respiration and some of the factors influencing its control. Ferroni [8] in 1899 published a graphic record of rhythmic movements obtained from the maternal abdominal wall and six years later, Ahfeld [1] demonstrated the same thing. Both authors were of the opinion that these movements were respiratory ones, but at the time, no interest was taken in their work and the results were ignored. It was not until 1937 that Snyder and Rosenfeld [22] were able to demonstrate respiratory movements in animals by exposing the fœtus under physiological conditions and directly observing it. The animals that they used were the guinea-pig, rabbit and cat, and, later, Barcroft [3] confirmed this by direct observation on the sheep. The conclusions of these writers are important, because by their study of intra-uterine respiration in animals they were able to demonstrate some of the factors controlling it. Firstly, that excess of carbon dioxide to the mother does not stimulate fœtal respiration, whereas a lack of it produces inhibition. Secondly, that the fœtus is very sensitive to the effects of narcotics and respiratory movements are abolished at a level of analgesia which does not impair maternal respiration. Snyder and Rosenfeld [22] also showed that anoxia in the fœtus never produces the initial respiratory stimulation, such as is seen in the adult, but is depressant in its action. From this, they concluded that the carotid body reflex is not present in the fœtus. This depressant effect of oxygen lack in the fœtus is logical because, were it not so, the actual process of labour might stimulate the fœtus to initiate big respiratory movements and so drown itself. As Barcroft [4] has pointed out, the fœtus behaves quite differently from the adult and it may be dangerous to make assumptions about the effect of anything on the one from the known effect on the other.

It is not yet clearly understood why the newborn child takes its first breath at all and having done so, why it continues. Preyer [19] in 1882 thought that the onset of respiration in the newborn was due to some nervous stimulation, such as contact of the skin with air. That stimulation of the fifth cranial nerve in the sheep fœtus will initiate gasping respirations has been shown by Barcroft [3]. The sudden freedom from continuous pressure immediately after birth may be a factor, but this would appear unlikely because in birds the newborn chick takes its first breath from the air sac at the top of the egg before breaking out of the shell, so that here the release of pressure occurs after respiration has started. Anoxia plays no part in the initiation of the first breath. This is demonstrated clinically by the fact that blue asphyxial babies do not breathe at once.

The relative resistance of the newborn to the effects of oxygen lack is important. Robert Boyle [6] first commented on this in 1670 when he noted that very young kittens survived longer than their mothers under asphyxial conditions. The newborn rat will survive one hour in an atmosphere of nitrogen without apparent ill-effect and the newborn dog and cat twenty-five minutes [7]. The explanation of the resistance is not clear. Himwich and others [11] have shown that the newborn brain has a greater store of carbohydrate than that of the adult and that this can be broken down anaerobically to provide energy for the cell. By injecting sodium iodoacetate, which prevents the breakdown of carbohydrate, into young rats and immersing them in nitrogen, they showed that their survival time was greatly diminished. In another series of experiments they found that hypoglycæmia reduced the survival time in nitrogen, whereas an increase in glucose prolonged it.

Another explanation for the resistance of the newborn to anoxia is that the fœtus may have a more efficient system of oxygen tissue enzymes than the adult which disappears within a few weeks of birth. In cyanotic congenital heart disease this resistance is maintained and although these children may remain undeveloped physically, mentally they are normal. They are also relatively resistant to the effect of the barbiturates and will tolerate twice the ordinary child dose without ill-effects. As barbiturates exert their action by inhibition of carbohydrate oxidation, it is possible that in the cyanotic child there is some alternative enzyme system which "boosts up" nerve cell respiration.

There are three fundamental causes of neonatal asphyxia: Intra-uterine trauma, fœtal anoxia, or maternal narcotics. White asphyxia is a more severe stage of the blue variety and

may be described as a state of severe shock. Windle and Becker [24] have shown that if the umbilical cords of full-term guinea-pigs are occluded for periods up to eight minutes, then the animals showed all the signs of blue asphyxia; longer times produced the white state. This change over from blue to white is sometimes produced in the very young under inadvertent asphyxial conditions. In the early stages the child is very cyanosed with a high blood pressure and a good pulse, but soon respiration fails completely. After a few minutes of respiratory arrest, the child suddenly becomes pale with an imperceptible pulse and appears to be near death. The exact mechanism of this is unknown, but probably in blue asphyxia the heart attempts to compensate by increasing its output, later a circulatory crisis occurs and the output falls. This explanation is true for the effect of anoxia on the heart of adults [23]. Narcotics, by depressing fœtal respiration and probably delaying the onset of the first extra-uterine breath, predispose to either blue or white asphyxia.

It is accepted that anæsthetic agents do produce a delay in the onset of newborn respiration. Any narcotic which has an analgesic effect on the mother must be depressant to the fœtus because narcotics achieve their action by an histotoxic anoxic effect on the central nervous tissue [20]. In spite of this, much clinical research is being carried out to find an analgesic drug which will eliminate the pain of childbirth but have no depressant effect on the baby. It is unlikely that such a drug will be found unless it is one that has so complex a molecular structure as to be too big to pass through the placental barrier. So far, all the present known analgesics are carried into the fœtal circulation. Because the fœtus absorbs a relatively large proportion of any anæsthetic agent given to the mother, the best of those now in use would be one which was either excreted quickly by the newborn baby or else destroyed. All the lipoid soluble drugs should be avoided as they are excreted via the lungs, but if they are used, chloroform, being the most potent, is the most efficient. The best agents are the gaseous ones, either nitrous oxide or cyclopropane. Nitrous oxide has two advantages. Firstly its method of administration is simple; secondly, any pure asphyxiating agent will have less effect on the fœtus than on the mother because of the difference in the dissociation curves of the two types of hæmoglobin, maternal and fœtal [15]. In 1941 Fazekas and others [7] showed that rat fœtuses delivered from mothers who had been killed with 5% oxygen in nitrous oxide respired spontaneously at birth. In favour of cyclopropane, a high percentage of oxygen can be given, so that at birth the newborn child should be fully oxygenated and its respiratory centre will only have to counteract the narcotic effect of the anæsthetic agent without the depressant action of ordinary anoxia. But, as the increase in maternal blood oxygen saturation will be small, the advantage to the fœtus will be minimal.

There are a number of other drugs whose analgesic properties in obstetrics might be investigated. The effect of intravenous novocain is not completely explained and its action may be partly peripheral. Some of the antihistamine group, e.g. benadryl, have considerable hypnotic activity and it would also be interesting to study the effect of some of the autonomic nervous system blocking agents, such as tetra-ethyl-ammonium bromide or the methonium compounds on obstetric pain.

The best method of resuscitation of the newborn must vary with the cause of the asphyxia. In the case of the blue variety, attempts should be made to cause maximum nervous stimulation of the respiratory centre so that the baby will expand its lungs of its own accord. The time-honoured method of stimulation of the skin, either by tactile or temperature change, is logical. Analeptics are to be condemned because unless they achieve their result immediately they stimulate the brain to produce a greater oxygen debt than it already has. The widespread use of analeptics in resuscitation has been cited [12] as a good example of the enormous resistance of the newborn to anoxia.

The administration of oxygen through a nasal catheter is valueless because the amount that can be absorbed through the mucous membrane of the pharynx must be very small. If it does achieve any effect, it is probably due to the nervous stimulation of the pharynx by the cold stream of gas. The protagonists of this method argue that when the infant does breathe, it will inspire pure oxygen. This is fallacious because, at the first gasp, the flow rate into the lungs will be rapid, much more than the 2–3 litres a minute passing through the catheter. Hence the oxygen will be enormously diluted with air. If oxygen is given, some form of mask and reservoir bag should be used.

Whether or not the umbilical cord should be clamped as soon as the child is delivered is a debatable point. Immediately after delivery there will be a small amount of oxygen obtained from the placental circulation. On the other hand, there is the stimulating effect of the clamp. It can be argued, with reason, that in the resuscitation of blue asphyxia there is no need for haste because the child's general condition is good. This is not true for the white variety, where there is a state of shock which should be treated by anti-shock measures. Presumably the cardiac output will be minimal and some method of increasing it, for example by transfusion, should be effective. Stimulation of the heart by itself is useless because in the shocked state there is an inadequate return. An auto-transfusion can be carried out by lowering the

baby several feet below the level of the mother before clamping the cord, so partially draining the placenta.

If the baby is known to be suffering from the effects of maternal narcotics, it is not only necessary to initiate the first breath, but also to continue stimulation to counteract the depressant effect of the narcotic. Here the analeptics may be of value, but after the first breath, which will expand the lungs, some mechanical device, such as a small Drinker apparatus, can be used [17]. The use of positive pressure ventilation is not without danger unless there is very accurate control. Owing to surface tension effects, the pressure necessary to inflate the atelectatic lung is greatly in excess of that needed to ventilate aerated tissue and, in lungs which may be partially expanded, this may disrupt already open alveoli without having any effect on the atelectatic parts. It is interesting to note that when a Drinker apparatus is used to inflate the lungs of a stillborn infant, the pressure needed is very high, much higher than that which the newborn could possibly achieve by itself [2]. How then does it manage to open its lungs at all? It may be by gradual active dilatation of its bronchial tree, starting at the larger bronchi and moving downwards with a wave-like motion so overcoming the surface tension effects and allowing the lungs to expand easily. This must be a nervous mechanism.

Carbon dioxide as a stimulant in the newborn is useless because not only has it been shown that high concentrations depress fœtal respiration, but also the respirationless child will already have a high body carbon dioxide.

Prophylactic measures might be of value in the treatment of asphyxia of the newborn. When analgesic drugs are used, a state of potential respiratory depression in the baby can be forecast. There may be evidence before birth of anoxia, the so-called fœtal distress. Under these circumstances, initial respiration at birth may be inhibited and if some method of preventing this could be found, it would be of great practical value. The protective influence of carbohydrate on the brain has been mentioned [11]. Suitable maternal diet in the later stages of pregnancy might increase this store in the fœtus. Again, intravenous glucose might be of use in the treatment of fœtal distress. Oxygen enzymes, such as cytochrome-c, might be of value to the mother in labour in the hope that they will pass into the fœtus and so enable it to utilize its oxygen more effectively. This has not been attempted yet, but cytochrome-c has been given to newborn guinea-pigs in an attempt to increase their survival time in nitrogen. So far the results have been somewhat equivocal [5].

The administration of oxygen to the mother will be valueless if it is only done for the last few minutes prior to the birth of the child because the giving of pure oxygen to the normal individual only increases the saturation of the blood from 98 to 100%, so that the effect of this on the amount in the fœtus would be small in spite of the different dissociation curve of fœtal hæmoglobin. But if it is given over a long period, then the nitrogen in the body will be eliminated and oxygen will replace it in the tissues both of the mother and of the fœtus, hence a bigger store will be available when the child is born. That the prolonged administration of oxygen does eliminate nitrogen from the body was demonstrated during the last war when it was used as a method of preventing "bends" due to the nitrogen bubbles which occurred at high altitudes in aircrew [9].

Regarding the effects of newborn asphyxia, much work has been done to show that it can cause permanent mental damage. Schreiber [21] collected 900 children who had had some evidence of asphyxia at birth and attempted to demonstrate that they had a higher incidence of mental defects than normal. Preston [18] in another series showed that they were mentally retarded. But in neither is the degree of asphyxia defined and the cases are not controlled statistically. Also the pathological picture that Schreiber [21] describes is in no way conclusive. Lund [14] noted a striking increase in postnatal complications in the asphyxiated babies in a series of two thousand deliveries. These three authors, however, all fail to mention the other factors of birth trauma and heredity in relation to mental development. In direct contrast, McPhail and Hall [16] found no evidence of mental abnormality related to asphyxia at birth in a group of 270 children. Again, Keith and Norval [13] followed up 111 children for four years, who suffered from neonatal asphyxia, and were unable to demonstrate any deviation from normal.

Since the newborn are so resistant to anoxia, it is unlikely that asphyxia does materially affect mental development, but final proof must await the result of an experiment with a large number of children, followed-up from the moment of birth until the age of 7 and the results assessed statistically, bearing in mind other variable factors such as heredity and the intelligence quotients of both parents; this is being done. An alternative would be to breed animals successively and selectively who have been subjected to asphyxia at birth and discover whether there were any mental deterioration.

Experimentally, pathological nerve-cell changes have been described [24] in full-term fœtuses deprived of oxygen by clamping the umbilical cord. This work, however, is not strictly comparable to that of ordinary newborn asphyxia because the animals were not only

deprived of oxygen, but also of any nutrient to their brain cells, so that anaerobic respiration could not take place. Nerve-cell changes following asphyxia are very difficult to assess from a histological viewpoint. Trauma to the brain while removing it, bad fixation or alterations in temperature prior to fixation, will all produce pseudo-anoxic changes. So any experimental evidence offered must be controlled under the most stringent conditions; with human material perfect control is impossible.

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Mr. P. M. G. Russell (Exeter) showed a mechanical rocker designed to combine the principle of Eve's method of resuscitation with Gibberd and Blaikley's method of intratracheal oxygen which was in use at the Royal Devon and Exeter Hospital. The instrument was largely devised by Dr. Geoffrey Kelly of Torquay while resident anæsthetist and obstetric house surgeon at the hospital. The rocker is driven by an electric motor and incorporates a mechanism so that oxygen flows at a measured pressure during the inspiratory phase, i.e. while the baby's feet are descending, but is cut off on the reverse or expiratory phase when the abdominal viscera are pushing the diaphragm upwards.

The apparatus seemed to provide a method of resuscitation which was active without being violent and the results so far had been encouraging. What was so impressive was to see a pink colour gradually replace the previous pallor and cyanosis in the baby's face and when the motor was switched off the baby was found to be breathing tranquilly.

Mr. A. H. Charles favoured endotracheal insufflation with oxygen for anoxic babies when they did not respond to simple measures. He emphasized the need to have the apparatus ready, though it was seldom used, and showed photographs of a tilting platform upon which the baby is placed so that its head is level with the operator's chin. The baby is horizontal for the passage of the endotracheal catheter to which a two-way adaptor is fitted. The baby's head is lowered for tracheobronchial aspiration. By means of the two-way adaptor aspiration and oxygen insufflation can be carried out through the same endotracheal catheter.

Professor W. C. W. Nixon asked Dr. Morison if the hyaline membrane which he had found in the alveoli was present only in immature babies. He disagreed with Dame Louise McIlroy in her condemnation of pituitrin. Provided uterine contractions were properly recorded, the use of an intravenous pituitrin drip was very helpful in cases of inco-ordinate action of the uterus.

Dr. Morton, in reply, said hyaline membranes, though not lim ted to premature infants, were much more frequent in them. He attributed this to their greater chance of aspirating vernix debris, because anoxic complications more often arose before their membranes ruptured, and to their less satisfactory elimination of the debris from their air passages after birth.

Section of Urology

President—Professor CHARLES WELLS

[*March* 23, 1950]

Streptomycin in Urinary Tuberculosis

By ARTHUR JACOBS, F.R.F.P.S.G., and WALTER M. BORTHWICK, Ch.M.

THE object of this communication is to present some of the results obtained so far in a controlled trial of streptomycin therapy for tuberculous disease of the urinary tract. This investigation commenced at Robroyston Hospital, Glasgow, fifteen months ago under the auspices of the Tuberculosis Research Unit of the Medical Research Council and still continues. To date ninety patients have been studied. Selection of the cases for streptomycin treatment is made from a sequence of numbers taken from a statistically prepared list kept at the M.R.C. office where the name, age, sex and category of each patient is sent. Streptomycin has been given to 46 patients and 44 have been used as control cases.

It was decided at the outset to group the patients into five categories.

Group 1: Unilateral renal tuberculosis—minor lesion without cystitis.
Group 2: Unilateral renal tuberculosis—major lesion necessitating nephrectomy: cystitis.
Group 3: Bilateral renal tuberculosis—nephrectomy for the more advanced lesion.
Group 4: Tuberculosis occurring in the remaining kidney subsequent to nephrectomy for unilateral disease.
Group 5: (*a*) Major bilateral tuberculous lesions.
(*b*) Minor bilateral tuberculous lesions.

These categories comprise all varieties of renal tuberculosis excepting those suffering from tubercle bacilluria without a demonstrable renal lesion and those with unilateral lesions who become tubercle negative after nephrectomy. It was considered that it would not be possible to draw any conclusions, at least for many years, from the tubercle bacilluria group where no clinical lesions were demonstrated. It was also considered unjustifiable to withhold nephrectomy from patients with established clinical unilateral lesions and that no satisfactory information would be obtained by treating such patients with streptomycin if nephrectomy rendered them tubercle negative. A continuing residual cystitis with a tubercle positive urine however, places these patients in Group 2. Genital disease has not been studied unless it has happened to be coincidentally present.

The routine investigation carried out on every patient, whether treated by streptomycin or a control, is as follows. A tubercle positive urine is confirmed by direct smear, guinea-pig inoculation and culture. The separate kidney urines are similarly examined where their collection is possible. These tests are made before commencing treatment, on occasions during treatment, one month after completion of treatment and at two-monthly intervals during the follow-up which still continues. Cystoscopic and pyelographic (excretory and retrograde) examinations are likewise made before and after treatment. Intravenous urography by itself is inadequate for the demonstration of early lesions. Tests for streptomycin resistance are routine and assays of streptomycin levels in the blood are carried out. Observations on toxic effects with particular reference to vestibular damage are also made. It will be appreciated that an invesitgation of this nature entails a magnitude of work which is only possible by the combined efforts of an organized team.[1]

The patients treated by streptomycin are given 1 gramme daily in two intramuscular injections for ninety days. Controls and streptomycin-treated patients receive similar general medical treatment; tuberculin is not given to either set of cases.

Results.—In this preliminary report we are limiting our observations to the effects of the therapy on the urinary tract as ascertained by repeated bacteriological assays and by preliminary and follow-up cystoscopic and pyelographic examinations.

GROUP 1.—It is required of patients placed in this group that the lesion be a small one, yet demonstrable by pyelogram and that no appreciable clinical or cystoscopic bladder changes should have taken place. It was considered that this group would offer particularly favourable scope for observing the effects of streptomycin. A total of 15 patients were

[1]The following were the members of the team: Dr. A. M. Foulis, Physician—Superintendent, Robroyston Hospital; Mr. Arthur Jacobs, Consultant Urologist; Mr. Walter M. Borthwick, Tuberculosis Consultant; Dr. John C. Dick, Pathologist. Much assistance was also given by Dr. W. G. Wimsett, Senior Registrar and Dr. McKinlay, Oto-laryngologist.

classified as belonging to Group 1 and of these 7 received streptomycin and 8 were control cases.

Streptomycin cases.—Of the 7 patients treated by streptomycin, 6 became tubercle negative during treatment. One month after the cessation of treatment, one of these 6 had reverted to tubercle positive; three months after treatment another had reverted and in six months still another had become tubercle positive. Thus in a period of six months after the termination of treatment, 3 of the 6 cases which had first been converted to a tubercle negative phase, reverted to a tubercle positive one. It was noted that the 3 showing this favourable response had minimal pyelographic changes. In fact, if one had not been aware of a tubercle positive urine the pyelograms alone would not have sufficed for the diagnosis of a renal tuberculous focus.

The urine of the contralateral kidney became tubercle positive during or after treatment in 3 of the 7 patients and one developed cystitis. With regard to pyelographic changes, it was found that in one case the lesion had increased, whilst in one other the cavity tended to become shut off. The following is an account of the latter case:

A. S., male, aged 44. *Group* 1

This patient was admitted to hospital with a tuberculous elbow joint and found to have pyuria with a tubercle positive urine though without symptoms referable to the urinary tract. The bladder was of normal capacity and no cystoscopic changes were apparent. On pyelography the moth-eaten appearances of the upper calyces of the right kidney indicated a localized ulcero-cavernous lesion (Fig. 1). The urine from the right kidney was tubercle positive. The pyelographic appearances of the left kidney were normal and its urine was tubercle negative.

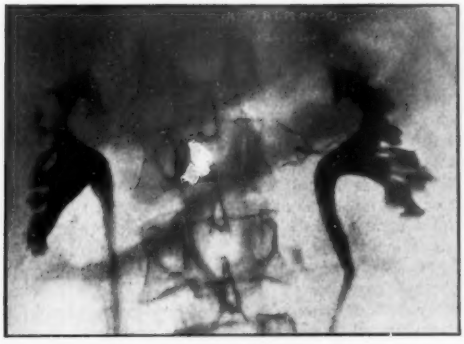


FIG. 1 (*Case A. S.*).—Bilateral retrograde pyelogram showing moth-eaten appearances of upper calyces, right kidney, indicating a localized ulcero-cavernous lesion.



FIG. 2 (*Case A. S.*).—Bilateral retrograde pyelogram one month after completion of treatment. The lesion in the right kidney has apparently become shut off.

Streptomycin treatment was commenced on March 21, 1949, and completed on June 18. One month later, retrograde pyelography indicated that the lesion had become shut off (Fig. 2). The pyuria had cleared and both kidney urines were tubercle negative on animal inoculation. The bladder urine was, however, positive. Four months later, pyelography showed the cavity in the upper pole still shut off but the kidney urine had reverted to a tubercle positive one (Fig. 3). There was no deterioration in the bladder, the elbow-joint lesion showed marked improvement, he had gained weight and the vestibular function was normal. Now, eight months after cessation of treatment, the left kidney urine as well as the right is tubercle positive and the pyelogram suggests the appearance of a lesion connecting with the upper calyx of the left kidney. The appearances on the right side are as before (Fig. 4).

It is apparent that the infundibular opening into the upper group of calyces of the right kidney has become constricted but not completely occluded and that the tuberculous focus itself has remained active. Treatment has not prevented the appearance of a tubercle positive urine in the contralateral kidney.

Control cases.—Conversion of the urine to tubercle negative occurred in only one patient, the total period of observation in this instance being three months. The urine of the contralateral kidney became tubercle positive during the period of observation in 2 of the 8 patients, while 4 developed cystitis. A deterioration of the lesion as shown by pyelograms was manifest in 4 instances. These results are summarized in Table I.

TABLE I.—GROUP 1

No.	Conversion of urine for more than six months	Developed cystitis	Involvement of other kidney	Pyelographic changes: Improved	Pyelographic changes: Worsened
S.7 ..	3	1	3	1	1
C.8 ..	1	4	2	—	4

S=Streptomycin C=Control

GROUP 2.—In Group 2 were the patients who suffered from a unilateral renal lesion with associated cystitis. Each patient had the tuberculous kidney removed soon after the initial investigation had been completed and the operative procedure was always the same, being that of nephrectomy without ureterectomy.

Up to the present 25 patients in this group have completed a stay in hospital exceeding four months, so that each case has had at least one examination after the standard period of ninety days, whether that period was passed as a control or was spent under active treatment by streptomycin. In ten instances the follow-up examinations have been carried out more than six months after the observation period. Fourteen of the 25 patients were treated by streptomycin and 11 were control cases.

Streptomycin cases.—Of the 14 who had streptomycin, 5 were females and 9 were males. Conversion of the urine from positive to negative occurred in 12 and so far no reversion has taken place. The conversion was found in all these patients one month after the completion of the treatment and has persisted for three months in 3 and for six months in 1, and in 4 patients no tubercle bacilli have been detected in the urine during the eight months which have elapsed since the streptomycin treatment was discontinued. In the 2 patients who did not have a conversion of the urine, the tubercle bacilli have persisted for one and three months respectively after the cessation of treatment.



FIG. 3 (*Case A. S.*).—Bilateral retrograde pyelogram five months after completion of treatment. The focus in the right kidney is discernible but remains occluded.

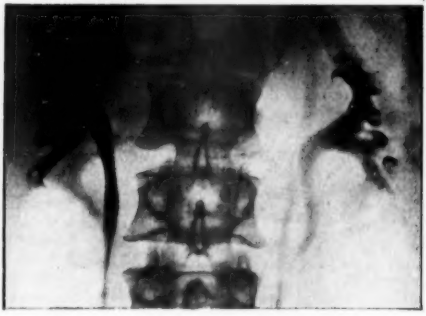


FIG. 4 (*Case A. S.*).—Bilateral retrograde pyelogram eight months after completion of treatment. The communication with the cavity in the upper calyx is still constricted. There is now evidence of an early lesion connecting with the upper calyces in the left kidney.

Cystitis was present in each of the 14 patients who received streptomycin and examination after treatment showed definite signs of improvement in 11 instances. In one other case the bladder mucosa was unchanged and in 2 cases of severe cystitis marked contracture of the bladder occurred soon after the start of treatment and cannot be interpreted other than as a worsening of the clinical state. This contracture persisted after the course of streptomycin was finished and was so marked that the patients were considered to be in need of transplantation of the ureter into the bowel. Of the 11 patients whose bladder condition improved the initial examination had shown slight cystitis in 5, moderate cystitis in 5 and severe cystitis in 1. The bladder mucosa became normal in appearance in 9 instances, 5 of which had previously shown slight cystitis and 4 moderate cystitis. In the 2 patients who did not have a conversion of the urine, the bladder mucosa was unchanged in 1 and greatly improved in the other.

None of the 14 patients has up to the present developed disease of the remaining kidney.

Control cases.—The 11 patients in this group, 5 females and 6 males, did not have streptomycin treatment for renal tuberculosis. The only one who received streptomycin was a man

who developed tuberculous meningitis and miliary pulmonary spread soon after the observation period started, but treatment was unsuccessful.

In the 10 remaining patients the initial examination showed the cystitis to be slight in 3, moderate in 3 and severe in 4. Conversion of the urine occurred in 2 of the 10 and has remained so for six and eleven months respectively. Both patients had an initial slight cystitis. Tubercle bacilli persisted in the urine of 8 cases, in 7 of which the cystitis was unchanged. The remaining person showed some worsening of the slight bladder disease.

In 2 of the 10 patients the remaining kidney became tuberculous during the period of observation. One of these patients died of uræmia after refusing any form of treatment. These results are summarized in Table II.

TABLE II.—GROUP 2

No.	Conversion of urine	Cystitis			Spread to other kidney
		Improved	Worsened	Unchanged	
S.14 ..	12	11	2	1	0
C.10 ..	2	2	1	7	2

S=Streptomycin C=Control

The number showing conversion of the urine seems to be significant in this group of streptomycin-treated patients, but the numbers are too small to comment on protection of the remaining kidney. Improvement of cystitis can also be expected in the majority of cases, although it appears that in patients with a greatly reduced bladder capacity and severe cystitis, one must be prepared for a marked aggravation of micturition which may persist after the cessation of streptomycin. A graph showing the diurnal and nocturnal frequency of micturition in the 2 patients who had contracture of the bladder rose sharply soon after the start of treatment, and the following case is worthy of note.



M. A., female, aged 24. *Group* 2

This girl had a right nephro-ureterectomy in Robroyston Hospital in December 1947. She was readmitted at the end of 1948, because of a persistently positive bladder urine.

Examination in January 1949 showed a bladder capacity of 14 oz. and a shallow elongated ulcer between the ureteric orifices. The urine from the left kidney was negative and normal pyelograms were obtained. She was placed in Group 2 and she became a control case.

Repeated examinations showed that by August the bladder capacity had been reduced to 8 oz. but by October some improvement was noted. On October 14, 1949, a course of streptomycin was started outwith the controlled investigation. Almost immediately, frequency of micturition was greatly intensified, occurring at 15 to 20 minute intervals. Both vestibular nerves were damaged after one month and the drug was stopped after two months. One month after the cessation of treatment, the patient felt well and was able to walk during the day without unsteadiness, compensating for vestibular dysfunction by vision. Urination was necessary every 15 minutes but the bladder urine did not contain tubercle bacilli. Urographic examination showed a contracted bladder and consequent back pressure dilatation in the ureter and renal pelvis of the remaining kidney (Fig. 5). Transplantation of the ureter into the pelvic colon was therefore carried out.

In this case, streptomycin was followed by severe contracture of the bladder and gross vestibular damage. On the other hand, the bladder urine did not contain tubercle bacilli.

FIG. 5 (*Case M. A.*).—Retrograde cystogram made two years and three months after a right nephro-ureterectomy and one month after completing a course of streptomycin treatment. The pyelo-ureterogram, obtained as a result of regurgitation of the radio-opaque fluid from the bladder, shows moderate dilatation. This is due to back pressure, the kidney being uninfected.

GROUP 3.—Patients in this group suffered from bilateral renal tuberculosis with the disesae more advanced on one side indicating, in our opinion, removal of that kidney. The operation was the same in all cases being that of nephrectomy without ureterectomy. 12 patients, 5 females and 7 males, were placed in this category and 6 were given streptomycin therapy after the operative procedure.

Streptomycin cases.—Consideration of the 6 patients who had a course of streptomycin showed that conversion of the bladder urine from positive to negative for tubercle bacilli occurred in 3 instances and conversion of the solitary remaining kidney urine in 4 instances. The 3 negative bladder results have persisted for eight, nine, and ten months respectively, while the patient with the negative kidney and positive bladder urines has been examined at one, two and four monthly intervals since the cessation of the treatment.

Originally the remaining kidney lesion was not obvious pyelographically in 3 instances, was visible as a small lesion in 2 and as a moderate lesion in the remaining 1. Follow-up renal examinations showed that there was no alteration in the 3 normal looking kidneys, that a small lesion had apparently disappeared in 1, a small lesion was unchanged in 1 and that the moderate lesion had shown deterioration.

All 6 patients had visible cystitis before treatment and improvement after treatment was noted in 5 while the sixth was unchanged. The improvement amounted to a clearing of the bladder mucosa in 1 with previous slight cystitis, to slight from moderate cystitis in 4, while the 1 patient with severe bladder involvement showed no change after treatment.

Control cases.—In the 6 patients who did not have streptomycin there was no example of urine conversion. In all cases the bladder and remaining kidney urine specimens showed tubercle bacilli for a period varying from four to eight months.

At the beginning of the control period the remaining kidney lesions were visible by pyelography in 4 instances but could not be seen in 2. The lesions were all small and on re-examination it was found that in 2 cases an initial small focus had deteriorated and in 1 case where no lesion had been visible there now appeared a filling defect in the upper pole of the kidney. No alteration was noticeable in the remaining 3 patients.

Cystitis was classified as slight in 4 patients, moderate in 1 and severe in 1, before the observation period started. In the most recent examination, four to eight months afterwards, the cystitis was found to be worse in 3, unchanged in 2 and slightly improved in 1. These results are summarized in Table III.

TABLE III.—GROUP 3

	Conversion of urine		Cystitis			Kidney lesion		
No.	Bladder	Kidney	Improved	Worsened	Unchanged	Improved	Worsened	Unchanged
S.6 ..	3	4	5	0	1	1	1	4
C.6 ..	0	0	1	3	2	0	3	3

S=Streptomycin C=Control

Conversion of the urine in this group is also significant, although it probably depends to a great extent on the severity of the remaining kidney lesion and to a lesser extent on the degree of cystitis. What seems to be important is the fact that the conversions of the urine have persisted up to the present, although a prolonged follow-up will be necessary. It should be noted, however, that the conversion occurred in patients with a small lesion in the remaining kidney. In one case with a moderate kidney focus the disease worsened and the separate urinary specimens contained tubercle bacilli.

Again the findings indicate that an improvement in the cystitis can be expected in the great majority of patients. The disappearance of an obvious kidney focus seems an unlikely occurrence.

M. O., female, aged 22. *Group* 3

This patient had her left kidney removed in November 1948 after a previous examination had shown bilateral renal tuberculosis with the disease more marked on the left side. Excretion pyelography demonstrated the right kidney as a series of dilated calyces with a distended pelvis. On retrograde pyelography the calyces, pelvis and ureter were seen to be dilated. These changes were considered to be due to back pressure. The bladder capacity was under 7 oz. and the cystitis was noted as severe.

She also suffered from chronic bilateral pulmonary tuberculosis and investigation before streptomycin showed almost total destruction of the epiglottis with swelling of the right artytenoid and ulceration of the left ventricular band. These conditions were symptom-free and were considered to be compatible with a tuberculous process of long duration.

Streptomycin was started on December 6, 1948, and stopped on March 6, 1949.

Re-examinations were carried out one, five and seven months after treatment. Catheterization of the right ureter was never possible after the initial examination but on these examinations the bladder urine was persistently positive for tubercle bacilli. Excretion pyelography showed a worsening of the kidney lesion although there was slight improvement in the cystitis.

Streptomycin, in this case, did not prevent deterioration of a kidney lesion and it did not convert the urine. There was, however, slight improvement in the cystitis, marked improvement in the general condition and disappearance of the laryngeal ulceration.

W. McM., male, aged 19. *Groups* 1 *and* 3

Admitted with a left epididymitis and no urological symptoms, this boy was found to have a tubercle

positive urine. Investigation showed that he had a filling defect in the upper calyx of the left kidney, the urine from which contained tubercle bacilli. There was no cystitis and the patient was placed in Group 1. He was designated as a control case.

Six months later there was slight cystitis and the urine specimens from the bladder, right and left kidneys were all positive. As his primary control period was finished and he now qualified as a Group 3 case, his name was again submitted for consideration. Again he was a control case. Nephrectomy was carried out on the left side. Four months later, at the end of the control period, the bladder and right kidney urines still contained tubercle bacilli and the cystitis showed some worsening.

This patient is now having streptomycin and para-aminosalicylic acid but it is too early to assess the result.

This is probably a case in which many would give streptomycin while careful watch was kept on the urological condition, ready to step in at any time and remove the left kidney.

GROUP 4.—Six patients, 5 males and 1 female, were assessed as complying with the standards of Group 4. This group contained those patients who developed disease in the remaining kidney after a previous nephrectomy for renal tuberculosis. 4 of these patients received streptomycin.

Streptomycin cases.—The 4 patients who were treated with streptomycin all had severe cystitis and advanced disease of the surviving kidney. One man developed uræmia a fortnight after the onset of treatment and died within a week. In 2 of the remaining 3, frequency of micturition was aggravated during the course of streptomycin, being sufficiently severe in one to necessitate transplantation of the ureter, while in the third patient there was some improvement in the frequency of micturition.

In only 1 of the 3 cases has the urine shown conversion. That case, in which the ureter was transplanted, has remained negative up to the present, two months since the cessation of streptomycin. The specimen of urine from the divided ureter at operation failed to show tubercle bacilli.

The pyelographic appearances in all 3 have remained unchanged.

Control cases.—The 2 men who did not have streptomycin elected to discharge themselves from hospital. Both had ulcerocavernous disease of the single kidney with associated severe cystitis. Out-patient follow-up, many months after the first examination, showed marked deterioration of the renal and bladder conditions and the urine still contained numerous tubercle bacilli. These results are summarized in Table IV.

TABLE IV.—GROUP 4

	Conversion of urine		Cystitis			Kidney lesion		
No.	Bladder	Kidney	Improved	Worsened	Unchanged	Improved	Worsened	Unchanged
S.4 ..	1	–	–	2	1	–	–	3
C.2 ..	0	–	–	2	–	–	2	–

S=Streptomycin C=Control

Tuberculosis of the solitary remaining kidney was advanced in the cases under review and apart from slight improvement in the cystitis of one treated by streptomycin no changes were noteworthy. Aggravation of an already severe cystitis was again noted.

It appears that in this type of case, no lasting improvement can be expected with streptomycin and taking into account possible toxic effects, many may consider it inadvisable to give the drug.

GROUP 5.—At the beginning of the investigation it was decided to subdivide Group 5 into two, 5A and 5B. Patients suitable for 5A had major bilateral renal lesions for which no active measures were considered possible, while those eligible for 5B had small bilateral lesions of a minimal nature but lesions which could be seen on pyelograms. In that way patients with tubercle bacilluria were excluded. The number of patients who came under observation with bilateral minimal disease was very small and later the subdivision was abandoned. For interest, however, 3 patients in this subdivision will be included in the results.

The number admitted to Group 5 more than four months ago was 16. 8 of these patients, 3 female and 5 males, were given a course of streptomycin and one of the females came under the section of small bilateral lesions. The results are somewhat difficult to describe in detail, as in many instances catheterization of the ureters was impossible on account of the advanced bladder changes, and good excretory pyelograms were difficult to obtain because of the renal destruction.

Streptomycin cases.—2 of the 8 cases treated by streptomycin died before the urological condition was reinvestigated. One death was due to uræmia and occurred within three weeks of the start of the drug. It is impossible to blame the drug for precipitating death in this man with advanced renal disease as he had been in hospital for a long period with spinal tuberculosis and his condition had remained satisfactory until just before the streptomycin

was started. Despite signs of deterioration it was decided to give him the possible benefits of treatment. The other death occurred in a man with advanced renal disease and his death was considered to be due to an intracranial tuberculoma with associated meningitis. This lesion manifested itself two weeks after the cessation of his treatment before follow-up examination was due and unfortunately a post-mortem examination was refused. The histological examination of the kidneys after 90 grammes of streptomycin might have been of value.

Excluding the 2 deaths and the 1 patient with small bilateral lesions, 5 cases remain to be considered. Of these 5, 4 had advanced bilateral ulcerocavernous disease of the kidneys and re-examination up to six months after the end of the course did not reveal any obvious changes. The remaining patient, a female, had been under observation for some months before being admitted to the investigation. She suffered from a slight cystitis and had cavitation in the lower segment of the right kidney and a moth-eaten appearance of the upper calyx on the left side. One month after treatment, the bladder and left kidney urines were still positive for tubercle bacilli but three months afterwards all separate specimens were negative. The negative results were all confirmed at four and five monthly intervals after the streptomycin and the bladder were found to be normal.

The patient in Group 5B was a woman who on examination was found to have a dull lustreless bladder mucosa with a bladder capacity of 15 oz. Retrograde pyelography showed small lesions in both kidneys and the bladder, right and left kidney specimens all contained tubercle bacilli. One month after streptomycin, the bladder capacity was 20 oz. and all separate urinary specimens were negative. The examination was repeated four months later when again all the specimens proved negative.

Control cases.—Control cases in this group numbered 6 with major lesions and 2 with small lesions. Of the 6 with advanced disease, 2 died within a short time of the start of the investigation, 1 of uræmia and the other of cerebral hæmorrhage. The remaining 4 all had severe cystitis with advanced renal disease. Re-examination four months to one year after admission showed that the renal disease was unchanged, the cystitis not improved and the urine still contained abundant tubercle bacilli.

The 2 patients with minor lesions were both re-examined up to a year after the start of the period of observation. The bladder mucosa, normal when first seen, was still free of disease at the end of a year. The retrograde pyelograms of one showed no alteration but several kidney specimens were all found to contain tubercle bacilli, while the retrograde pyelograms of the other showed lesions in both kidneys which had deteriorated and all separate specimens of urine were still positive to tubercle bacilli. These results are summarized in Tables V, VI and VII.

TABLE V.—GROUP 5

No.	Major lesions 5(A)	Died	Minor lesions 5(B)	Died
S.8 ..	7	2	1	0
C.8 ..	6	2	2	0

TABLE VI.—GROUP 5(A)

No.	Conversion of bladder and kidney urines	Cystitis		Kidney lesions	
		Improved	Unchanged	Improved	Unchanged
S.5 ..	1	1	4	1	4
C.4 ..	0	–	4	–	4

TABLE VII.—GROUP 5(B)

No.	Conversion of bladder and kidney urines	Cystitis		Kidney lesions	
		Improved	Unchanged	Worsened	Unchanged
S.1 ..	1	1	–	–	1
C.2 ..	0	–	2	1	1

S=Streptomycin C=Control

Again in this type of case, with obvious bilateral renal tuberculosis, the prognosis does not appear to have altered with the introduction of streptomycin. One case, which has been mentioned before, is worth demonstrating. The outlook in this girl has improved with streptomycin but continued observation is still necessary. It is noteworthy that the bilateral renal lesions in this patient were less advanced than those of the remaining patients in Group 5A.

E. McG., female, aged 21. *Group 5a.*

While under treatment for pleurisy in another hospital, renal tuberculosis was found to be present in January 1949. At that time cavitation was present in the lower segment of the right kidney but



FIG. 6 (*Case E. McG.*).—Bilateral retrograde pyelogram showing an advanced lesion in the right kidney and a focus connecting with the upper calyces of the left.



FIG. 7 (*Case E. McG.*).—Bilateral retrograde pyelogram two and a half months after completion of treatment. The diseased area in the lower pole of the right kidney is shut off.



FIG. 8 (*Case E. McG.*).—Bilateral retrograde pyelogram three months later. The communication with the lower pole is again patent.

specimens of urine from both kidneys were found on animal inoculation to contain tubercle bacilli. She was transferred to Robroyston Hospital at the end of May 1949. Examination there showed a slight degree of cystitis with bladder discomfort occurring with a content of 14 oz. Excretion and retrograde pyelography showed clubbing of all the calyces on the right side with constriction of the uretero-pelvic junction. On the left side the upper segment had a moth-eaten appearance with a constriction at its opening into the pelvis (Fig. 6). The X-ray and bacteriological findings confirmed a bilateral renal lesion but, in our opinion, there was no indication for removal of one kidney.

A course of streptomycin was started on June 24 and completed on September 21, 1949. One month after treatment, cystoscopy was repeated. The vesical mucosa now appeared normal and the bladder and separate kidney specimens were still positive for tubercle bacilli. Retrograde pyelograms were unchanged. Repeat urological examinations were carried out at two, four and six monthly intervals. The bladder capacity was then 22 oz. and the mucosa normal. Specimens of urine from the bladder, right and left kidneys were all negative. Retrograde pyelography showed that the lower segment on the right side was partly shut off in the earlier examinations but in the latest picture the lower segment was again open. On the left side there was an infundibular constriction to the upper calyx which had a moth-eaten appearance (Figs. 7 and 8).

This case has benefited from streptomycin but the observation period is too short to reach a definite conclusion. Vestibular function was unimpaired.

In patients with small bilateral lesions the outlook may be improved with streptomycin therapy. The following case seems to be an example of this.

Mrs. A. B., female, aged 32. *Group* 5*b*.

Examined in March 1949, she was found to have bilateral renal tuberculosis with a moth-eaten appearance of the upper calyces on the right side and clubbing of the terminal calyces of the upper group on the left side. The whole bladder mucosa was dull and lustreless with a capacity of 15 oz. without anæsthesia.

She was placed in Group 5B and streptomycin was started on June 24 and stopped on September 21.

Examinations one and four months after streptomycin demonstrated that the bladder capacity was over 20 oz. and all separate urinary specimens were negative for tubercle bacilli. Retrograde pyelograms were still abnormal but showed an improvement. Her general condition was greatly improved but there was marked vestibular dysfunction.

Summing up the results in Group 5, it is obvious that streptomycin cannot be expected to heal advanced lesions in a structure so highly organized as renal tissue. It seems reasonable to suggest that where lesions are so small that they could be replaced by fibrous tissue, as in Group 5B, streptomycin is not only justifiable but imperative when one remembers that this is a bilateral condition. This would also apply to patients with tubercle bacilluria.

Conclusions

The mode of this investigation was planned with the deliberate intention of eliciting all possible information of an objective character about the effect of streptomycin on the urinary tract infected by tuberculosis. As was mentioned at the outset of our communication the investigation continues and is likely to do so over a period of years. We consider, however, that as a result of our 15 months' experience, the following preliminary observations can be offered.

The treatment has no effect on an established caseocavernous renal lesion. This is not surprising for in spite of the high elimination of streptomycin by the kidney, a blood-borne therapeutic agent must, for the most part, be excluded from such an avascular focus. By encouraging fibrosis and consequent constriction there is a possibility that the focus, though itself remaining active, may become shut off. A regression of the constriction, however, can occur. Streptomycin therapy cannot therefore be recommended to supplant surgery and in clinical unilateral renal tuberculosis the diseased kidney should be removed.

We do not advise its automatic employment in all cases unsuitable for surgery. Thus when there is an advanced bilateral renal lesion or an advanced lesion in a solitary kidney, no improvement in the kidney lesion can be anticipated and vesical contracture may be accelerated.

From our experience with Group 2 cases, we consider streptomycin may prove beneficial as an additional therapeutic measure, possibly before as well as after surgery. Accepting Medlar's claim that in renal tuberculosis both kidneys at the outset are involved by minimal lesions, then after nephrectomy for a unilateral clinical lesion, streptomycin should diminish the risk of activation and development of the disease in the apparently healthy kidney. This statement is given with reservation, however, for in Group 1 cases the contralateral kidney became tubercle positive in 3 out of 7 treated cases whilst this occurred in only 2 out of the 8 controls.

Streptomycin does have a definite beneficial effect on secondary tuberculous cystitis but this would appear to be relative to the presence and degree of disease in the upper urinary tract. Thus in our Group 2 cases, that is those with a unilateral renal lesion who have been nephrectomized, cystitis has cleared and the urine has become tubercle negative in an appreciably larger number of streptomycin treated cases than has occurred with the controls.

With group 5 cases, however, consisting chiefly of patients with well-established bilateral

disease, no beneficial effect on the bladder resulted. In the few cases of Group 5 in whom the bilateral lesions were minimal, the effect of streptomycin on the bladder has been good.

It will be evident from the results we have so far obtained in this controlled trial, that the administration of streptomycin to those suffering from urinary tuberculosis is not an alternative to prolonged sanatorium care or to nephrectomy when the renal lesion is a unilateral one. Employed as an additional therapeutic measure, however, streptomycin may enhance a patient's chances of recovery.

ACKNOWLEDGMENT

The authors are indebted to the Tuberculosis Research Unit of the Medical Research Council for making this research possible and for supplying all the streptomycin required. They acknowledge with gratitude the help received from Dr. Marc Daniels and Dr. P. D'Arcy Hart in the planning of the investigation and in the assessment of the results.

The President said that in tuberculosis of the urinary tract the assessment of the effects of treatment and the comparison of one method with another was extremely difficult because the cases which one attempted to control were encumbered by so many variable factors.

He was a little disturbed concerning the suggestion that the intravenous pyelogram might not be good enough for diagnostic purposes. Most members had had the privilege of working in institutions outside their main teaching hospitals, and in some the radiological work was not of the standard found in the large general hospitals. Thus intravenous pyelography might sometimes prove unsatisfactory.

However, retrograde pyelography was not necessary in every case, and he deprecated the impression that it was necessary to make a retrograde pyelogram as a routine. The stereoscopic X-ray method with intravenous pyelography was worth while in cases in which the pyelograms were difficult to interpret.

One point of fundamental importance in this work was the relationship of the renal lesion to the general condition of the patient. He believed that cases needed in the first instance to be segregated into two big groups. The first group would consist of patients who had advanced, established, and progressive tuberculous lesions somewhere else—in other words, the sanatorium population—and who in the course of their illness developed renal lesions. These patients had a renal lesion as an incident in an infection which was likely to end fatally whatever was done for them.

The other group was that familiar to the ordinary out-patient department in the general hospital. These were people who came up complaining of increased frequency of micturition, and in whom tuberculous lesions of the urinary tract without gross disease elsewhere were discovered. Such patients might be expected to get perfectly well after suitable treatment. It was essential to clear the ground at the beginning by dividing the patients into those two groups.

With regard to the openers' statement that their patients had had the kidney removed but not the ureter, he asked why the more complete operation was not favoured, and how many such patients developed breaking down wounds subsequently.

He also asked in how many cases of patients in whom a tuberculous infection had returned after streptomycin treatment, the organisms had become resistant to streptomycin, and in how many the organisms were still sensitive.

Mr. E. W. Riches said that he considered the following cases were suitable for streptomycin:—

(1) Bilateral cases after nephrectomy on the worse side. The fact that tubercle bacilli had already been discovered on the relatively good side was not always a contra-indication to operation.

(2) Residual bladder lesions after nephrectomy.

(3) Cases with bladder lesions and a positive urine, but with no demonstrable renal lesion, or cases in which there was a doubt about the side of the renal lesion.

He asked about the post-operative prophylactic use of streptomycin in unilateral cases. If given it should be in a full course.

He had treated 16 cases, eleven of whom had been treated about a year or more ago. 10 of these were alive; the eleventh had miliary tuberculosis. In all these 10 cases there had been symptomatic improvement, but repeated search often revealed tubercle bacilli. A boy of 15 with a bilateral infection underwent nephro-ureterectomy and was given 50 grammes of streptomycin and 50 c.c. of moogrol. After six months twenty-four-hour specimens of his urine were taken; the first four specimens were all negative, but the fifth was positive.

Guinea-pig inoculation and culture entailed a lot of extra work for the bacteriologist but it was very necessary. It could not be said that a case was negative on the smear from a twenty-four-hour specimen alone.

He had been interested in the question of the contraction of the bladder and the ureter and whether it would improve or worsen on streptomycin. In a man with bilateral disease, left nephro-ureterectomy was done two years ago and he was given 90 grammes of streptomycin. The pyelogram taken eighteen months later showed the kidney to be rather more dilated and the ureter rather more tortuous, while the bladder was slightly more contracted. He was getting a back pressure kidney and he ought to have a transplantation. He was unwilling to come up because he was doing a full day's work as a motor mechanic. He suffered from the inconvenience of having to get up twice or three times in the night, but otherwise he was able to lead a normal life.

There had been one or two cases in which bladder capacity had increased. In one case after surgical treatment and streptomycin the bladder capacity for some time was only 5 oz., but had now increased to 16 oz., although the patient still had a positive urine.

There was one other point which must not be neglected, namely, the effect of streptomycin on the

vestibular apparatus. After 50 grammes, many patients got vestibular symptoms, and they were very miserable, being giddy in the daytime, and totally unable to stand up in the dark. Eventually they improved but he did not think they got well. He thought they must not lose sight of the occurrence of this damage, because unless they could be sure of some definite improvement in the renal tuberculosis by the use of this drug, it was in many cases a contra-indication to its use.

Mr. M. F. Nicholls said that he had the advantage of being urological surgeon to a large orthopædic hospital, and many of the cases he had to deal with came in the second group to which the President had referred. Renal tuberculosis came much more frequently from bone and joint tuberculosis than many people seemed to realize. Patients seemed to develop overt urinary tubercle when the bone and joint tubercle was on the way to healing. He had removed several kidneys after a full course of streptomycin, and the renal disease seemed to be unaffected by the drug.

He went on to describe one particular case. This was the case of a man whose spinal tuberculosis had virtually healed. He then developed frequency, and on cystoscopy was shown to have a minimal tuberculous ulceration of the bladder. The left ureteric orifice was diseased and would not admit a catheter. The right ureter was catheterized and proved tubercle-free. Owing to a technical fault in the X-ray installation, the ascending pyelogram could not be done. A course of streptomycin was started, and in a fortnight the bladder on further cystoscopy appeared entirely normal. Four months later, after the patient had had 50 grammes of streptomycin, he removed the left kidney which showed numerous pinhead lesions of the cortex, none of which encroached on the kidney pelvis or calyces which were normal. Histologically the tuberculosis was shown to be active in spite of the streptomycin.

Mr. D. S. Poole-Wilson said he had carried out streptomycin therapy on 14 cases. In 10 the treatment had been completed for some time and a tentative assessment of the results could be made. The dosage of streptomycin had been 0·5 gramme twelve-hourly for 120 days. As far as could be ascertained all the patients were free from active tuberculosis outside the urinary or genital tracts.

The patients fell into six categories:

(1) Bilateral renal tuberculosis with minimal but proven lesions in each kidney.

(2) Bilateral renal tuberculosis in which a major lesion on one side had been treated by nephro-ureterectomy and a small lesion is present in the remaining kidney.

(3) Unilateral renal tuberculosis—small lesions.

(4) Renal tuberculosis appearing in the remaining kidney after the other kidney and ureter had been removed for tuberculosis.

(5) Chronic tuberculous ulceration or cystitis persisting after removal of an infected kidney and ureter and in whom the remaining kidney appears healthy.

In connexion with this and the previous group the importance of nephro-ureterectomy in the treatment of renal tuberculosis was stressed. If a nephrectomy only is carried out a tuberculous ureteric stump may be left in situ and act as a focus for continued infection of the bladder. The presence of tubercle bacilli in the urine of such patients does not therefore necessarily indicate infection of the remaining kidney. In such cases removal of the infected ureteric stump may effect considerable improvement.

(6) Tuberculous sinus formation following operations on tuberculous kidneys.

The single patient in this group was a young boy, whose right kidney was removed on account of gross tuberculous infection. His condition did not warrant full removal of the ureter, which was as thick as a little finger. The wound subsequently broke down completely and refused to heal. Eventually the remainder of the ureter was removed and streptomycin therapy commenced. Subsequent healing was rapid.

In assessing the effects of streptomycin therapy it was noted that whereas tubercle bacilli were present in all the urines prior to treatment, at the completion of the course 6 were free of tubercle bacilli and in 4 the organism still remained present. After a matter of months, 2 of the 6 tubercle-free patients reverted and again showed tubercle bacilli in their urine.

Treatment had finally to be stopped in 1 patient owing to a severe urticarial reaction.

Vestibular symptoms were fairly severe. Some of the patients had a rather miserable time during the third and fourth months of treatment. During the early stages of treatment the patients were allowed out for short walks. By the third month some felt that they were not safe in going out alone and could not walk steadily in the dark; if blindfolded they could not maintain their standing balance.

Of the 9 cases receiving a full course of treatment, 5 showed marked clinical improvement. In 3 there was no appreciable change. From this small series it would appear that in about 40 to 50% of cases some clinical improvement will occur following streptomycin therapy. How long the improvement will be maintained is not known and some patients have paid a fairly heavy price in dizziness for the amelioration of their renal and vesical lesions.

Mr. Hugh Donovan said that he thought the paper to be a most important one, because it was an accurate and painstaking study of the effect of 1 gramme of streptomycin given daily over three months and because it showed that this dosage was quite inadequate. A report from the Veterans' Bureau (1949) had described some very encouraging results from 2 grammes of streptomycin given daily for four months. The speaker had found that 3·2 grammes of streptomycin was too toxic, and following the principle of naval gunnery he estimated that 2 grammes a day would probably prove to be the correct dose. He drew attention to a recent address by Dr. Geddes, given in Birmingham, in which the effect of simultaneous administration of P.A.S. was described. It seemed that this drug prevented the tubercle bacilli becoming resistant to streptomycin. Mr. Donovan concluded by pointing out that it was generally held to be dangerous to do an ascending pyelogram on a tuberculous kidney, and asked whether this might not have been responsible for some of the relapses in Mr. Jacobs' series.

REFERENCE

LATTIMER, J. K., AMBERSON, J., and BRAHAM, S. (1949) *J. Urol.*, **62**, 875.

Mr. R. Marcus described 28 cases (with numerous illustrations) which had been treated since November 1948 and which he had classified into four groups according to their character (Table I).

TABLE I.—STREPTOMYCIN IN URINARY TUBERCULOSIS

Condition	No. of cases	*Analysis of Results* Beneficial effect	Unaffected	Deaths	Remarks
1. Post-operative wound infections	7	6	1	nil	2 cases wound excised. 1 case skin grafts
2. Renal tuberculosis (unoperated)					Death due to:
(*a*) Early unilateral	3	2	nil	1	lobar pneumonia after discharge
(*b*) Bilateral	2	nil	1	1	renal failure
3. Post-nephrectomy cystitis					
(*a*) Alone	10	10	nil	nil	
(*b*) With back-pressure requiring ureteric transplant	2	1	nil	1	Death due to carbuncle of kidney
(*c*) With disease of 2nd kidney	2	1	1	nil	
4. Cases with open pulmonary lesions					
(*a*) Early unilateral renal disease					2 cases included in 2(a)
(*b*) Bilateral renal disease					Treatment disallowed 1 case
(*c*) Post-nephrectomy cystitis	2	1	1	nil	Considering resection of lung and ureteric transplant
Total	28	21	4	3	

TABLE II.—TUBERCULOSIS INFECTION OF GENITO-URINARY WOUNDS

	Condition	Initial streptomycin sensitivity	Dosage grammes	Total dosage grammes	Streptomycin resistance and sensitivity	Toxic effects	Additional surgery	Result
117709 O. N.	TB renal wound	1/2 unit	1/2 b.d.	35	None 1/2 unit	None	Excision and suture	Healed in ten days but small sinus communicating with ureter subsequently developed
E. T.	TB ulcer in suprapubic region	—	1/3 q.i.d.	60	None	None	None	Permanently healed in three months
125246 H. T.	TB suprapubic and renal wound	—	1/3 q.i.d.	60	None	None	Excision and suture of renal wound	Renal wound healed by first intention. Suprapubic wound healed in seven weeks
T. F.	TB renal wound 2nd attempt at suture failed	—	1/3 q.i.d.	60	None	None	None	Not materially affected
129029 G.K.W.	TB renal and suprapubic wounds	—	1/2 b.d.	120 (including local)	None	None	Renal wound skin-grafted	Skin graft partially successful. Suprapubic wound healed
116021 J. E.	TB vasostomy wound	1 unit	1/2 b.d.	60	Yes 32 units	None	None	Healed in seven weeks
99599 M. W.	TB ulcer vault of vagina	—	1/2 b.d.	70 (including local)	None	Mild Recovery	None	Healed in twelve weeks

Group 1 (7 cases) consisted of post-operative wound infections (Table II). He showed a number of slides illustrating the beneficial effect of streptomycin in these cases. Some wounds were excised and sutured under an "umbrella" of streptomycin. Primary union occurred. In one case skin grafts were applied. The grafts took and consolidated while streptomycin controlled the infection. Epithelialization continued after stopping streptomycin.

Group 2 (5 cases) were unoperated cases. Two early unilateral renal cases appeared to benefit from streptomycin.

Group 3 (14 cases) were cases with cystitis persisting after nephrectomy. A beneficial effect was noted in 10 cases.

Group 4 (4 cases) consisted of cases complicated with open pulmonary tuberculosis. One of these cases was refused treatment because the chest lesion was of the type which was known to respond unfavourably to streptomycin.

In this series of 28 cases the dosage of streptomycin had ranged from 10–120 grammes (Table III).

TABLE III.—STREPTOMYCIN IN GENITO-URINARY TUBERCULOSIS

Total Dosage of Streptomycin Used

Dosage in grammes	Number of cases
10	1
35	1
42	1
60	24
120	1

The first case (cystitis persisting after nephro-ureterectomy) treated with streptomycin was given only 10 grammes. The effect was satisfactory.

Of the complications (Table IV), hæmaturia occurred in two cases during treatment and was also noted later in a third case. A resistant strain of tubercle bacillus appeared in 4 cases—in 1 case in the fifth week, in 2 cases in the seventh week, and in the remaining case in the ninth week.

TABLE IV.—STREPTOMYCIN IN GENITO-URINARY TUBERCULOSIS

Complications Noted During Treatment of 28 Cases

Complications	No. of cases during treatment	No. of cases one year after treatment	Remarks
Exacerbation of symptoms	3	nil	Temporary
Mild back pressure changes	1	nil	
Gastro-intestinal disturbances	1	nil	Temporary
Vertigo	2	nil	Improved
Infective hepatitis and carbuncle of kidney	1	nil	Died
Deafness	nil	nil	
Myalgia	1	nil	Improved
Hæmaturia	2	2	
Renal failure	nil	1	Died
Pneumonia	nil	1	Died
Resistant strains of tubercle bacilli	4	nil	

Recently P.A.S. had been used. It was hoped that the synergic effect of antibiotics and chemotherapy might prove of value in genito-urinary tuberculosis.

Mr. David Band said that each of the five groups of clinical cases selected for streptomycin therapy had been covered by a comparable series of controls classified into similar groups, in which streptomycin was not used. The results in this investigation had been presented objectively and had been tabulated. It seemed that it was a fair challenge to invite Mr. Jacobs to say whether he thought streptomycin could replace the sanatorium as an essential adjuvant to the surgery of urogenital tuberculosis. Tuberculosis was a social problem, and would not be overcome by surgery, nor by the employment of streptomycin or any other antibiotic. It was a disease which had its beginning in childhood largely as a result of inadequate housing and faulty social conditions.

Mr. Walter M. Borthwick, in reply, said that the President had suggested that X-ray work in sanatoria was not quite up to standard. The sanatorium at which he worked accommodated almost 600 patients with tuberculosis and the quality of the X-ray work done by their radiological staff had reached a very high standard.

With tuberculous patients it was imperative that the pulmonary and non-pulmonary cases should not be in one unit and the number of renal cases outwith the genito-urinary unit, which was situated in the non-pulmonary section of the hospital, had been negligible; he could think of only one case at present which came into that category.

He agreed with what Mr. Nicholls had said about renal tuberculosis being frequently present in patients with bone and joint lesions. He saw a number of such cases, and, at present, out of 40 patients with renal tuberculosis, only 1 suffered from open pulmonary tuberculosis.

It was impossible to tell by intravenous pyelography every time there was a lesion in the kidney. Many of the cases were very clear, but there were others which required retrograde pyelography to demonstrate a small focus. One authority had mentioned epididymitis as a possible symptom of renal tuberculosis, and often in these cases the renal lesion was small and difficult to localize. It was in the obscure case with slight indications that they wanted to find out whether streptomycin was of benefit.

In his experience, most of the sinuses following nephro-ureterectomy were related to the abdominal wound and he wondered whether the removal of both kidney and ureter was not responsible for more complications.

Mr. Band had remarked that this was a controlled investigation. They had tried to treat the controlled case exactly the same as the one treated with streptomycin apart from the drug. The rise in the resistance was very important and he heartily agreed with one of the speakers who had mentioned a case of advanced pulmonary disease with a hopeless prognosis. They would also withhold streptomycin in that case. There was no case in this series with cavitation in the lungs.

As to the dangers of streptomycin, his patients were in bed for at least three months. He was surprised when Mr. Riches spoke of a definite improvement of vestibular damage within a year as he did not know there could be a recovery. If these patients were examined he thought it would be ound that unsteadiness did persist.

This investigation was undertaken under very strict rules: 90 grammes was the maximum dose to be given and no allowance was made for repeating the course. There was freedom of action after the observation period was over. Their dose of PAS was higher than had been mentioned in the discussion. They were giving 12 grammes a day but it was too early to give results.

Mr. Arthur Jacobs, also in reply, said that for routine investigation of the urinary tract in tuberculosis they were satisfied with intravenous pyelography follov ed by ureteric catheterization and the collection of urine from the apparently healthy kidney to confir.n that it was uninfected. But for the purpose of this investigation it had been felt that retrograde pyelograms would be required to portray changes taking place in a renal lesion. The employment of both methods in every case had confirmed this opinion, particularly for the delineation of the smaller foci. Contrary to what had been suggested by Professor Wells and to what is frequently stated, they were unaware of any evil sequelæ following retrograde pyelography in renal tuberculosis. He considered it was not without significance that not one of the discussants had attempted to demonstrate to the Meeting the progress of a lesion under treatment, by showing excretory pyelograms.

With regard to the question of nephro-ureterectomy rather than nephrectomy being the operation of choice, Mr. Jacobs indicated that the experience at Robroyston had been that nephrectomy alone was followed by a lower incidence of post-operative sinus formation than nephro-ureterectomy and that removing the complete ureter did not ensure resolution of a secondary cystitis. They had been rather disappointed with the effect of streptomycin on the bladder for although it might hasten a resolution of the secondary cystitis and even heal an area of ulceration the fibrosis associated with the healing process could result in a progressive contracture. Once this occurred it was irreversible and several cases in the series had, in consequence, required ureteric transplantation.

Concerning dosage it had been suggested that a larger amount than a gramme a day might be given and that the course should be longer than ninety days as in some of the trials reported from the U.S.A. He had, however, noticed in the more recent American literature a tendency to diminish the amounts, approximately to that used at Robroyston.

Finally in answer to Mr. Band he stated that in his opinion a sanatorium régime combined with nephrectomy when the disease was unilateral was still the most important method of treatment for renal tuberculosis. Streptomycin could be helpful but it had its limitations and might be dangerous. The equivocal results of the drug when given for renal tuberculosis were the justification for continuing the investigation as a controlled one and not giving streptomycin indiscriminately to every sufferer with a tubercle-positive urine. He hoped by this method that it would finally be possible to select the patients likely to benefit from the treatment and eliminate those whose condition might be worsened.

The President said that it was wise to avoid retrograde catheterization if possible, because of the undoubted, though admittedly small, risk of spreading infection. Everyone knew that if one took a patient with a septic infection and did a cystoscopy, a rigor might follow, and one visualized organisms in the blood stream with a constitutional disturbance. The same notion had to be entertained in the case of tuberculous infections.

When an intravenous pyelogram was necessary to clear up some doubtful point then the best moment to make it was when the patient walked into hospital. When patients had been in bed for a considerable period difficulties due to gas were greatly increased. Such inevitable difficulties were especially likely to arise in patients suffering from tuberculosis and confined to bed. He had himself had the privilege of working for many years in an institution devoted to the treatment of non-pulmonary tuberculosis and appreciated to the full the peculiar difficulties in this type of case.

[*April* 27, 1950]

The Renal Circulation [1]

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THIS Address was to have been a joint one by Professor Trueta and myself, but the calls which his new duties made upon his time prevented him—to my great regret—from participating[2]. I acknowledge my indebtedness to him and to my other colleagues in renal research, while stressing that they are not necessarily involved in the interpretations or views which I advance. My survey is shorter and less complete than I wish; also, according to the nature of scientific reviews, it is doubtless a mixture of elements which are lasting and of others which increase in knowledge will show to be ephemeral or incorrect. It may, however, serve some useful purpose as an unbiased interim account of a subject of physiological interest and clinical importance.

In the light of recent biochemical research upon what Schoenheimer (1946) so happily styled "the dynamic state of body constituents", the meaning of the word "circulation" needs to be extended so as to cover both the extravascular and the intravascular movements of water and solutes. The volume which so moves in and out each day is of the vast order of 7,000 litres (calculated from data in Flexner *et al.*, 1942), while the glomerular filtrate is about 180 litres and the output of urine about 1·5 litres. So the renal fluid excursion, contrary to what was generally thought but a few years ago (*see* e.g., Smith, 1943) is in fact *relatively* small. I mention this at the outset in order that the renal *blood* circulation, with which I am in the main to deal, may be envisaged in its proper relation to the total fluid movement of the body.

ONTOGENY

The physiological range is from conception to death, and we need to know what changes occur within that range in the renal vascular system and circulation, especially those of the human subject. The pronephric stage is virtually non-existent in mammals, nor is much known about the succeeding mesonephric one, but there is more information about the intra-uterine part of the metanephric stage which begins, before the mesonephric is over, at a fœtal age (in the human subject) of 4 to 5 weeks. The basal or juxtamedullary glomeruli, which are the first to develop and also the first (Morison, 1926) to be vascularized, begin to appear at 6 to 7 weeks, and are fairly fully formed at 10 weeks[3], while (Hewer, 1925) the glomerular basement membrane is well developed by 12 weeks. Cortical glomeruli are added in successive layers on the outside until the fœtus or newborn child has attained a weight of 4·5 to 5·5 lb. (Potter and Thierstein, 1943) and, presumably in correspondence with this, one can see an occasional large vessel in the cortex and considerable subcapsular vascularity[3]; the vascular loops of the outermost glomeruli are not so well-developed as those of the basal ones (Clara, 1936), and at times degenerate units are present in the subcapsular layer (Gruber; Peter, 1909; Peter *et al.*, 1927). In the fœtus the basal glomeruli are larger than the cortical ones—Külz (1899) gave the respective diameters as 138 μ and 99 μ (adult 240 μ); the glomerular tuft is completely covered by high cuboidal or columnar epithelium. Further anatomical details are that the cortex is narrow relative to the medulla, with the glomeruli close to one another in all three dimensions, and that (Daniel, 1947), in sections of the earlier stages, red blood corpuscles are much more numerous in the basal glomeruli and in the medullary vessels than they are in the cortex in general. The renal innervation in various mammalian fœtuses, including a 21 weeks' human one, is described by De Muylder (1948), who also gives references to earlier work. In the human subject, there is a very rich, mainly but not exclusively non-myelinated, supply reaching the kidney along the renal pedicle and the ureter and distributed, except for a few fibres to supporting tissue, essentially to blood vessels. The peri-arterial plexus supplies, *inter alia*, the afferent and efferent glomerular vessels and is in close relation to the macula densa; it misses the glomerular capillaries.

[1] Slightly abridged; to be integrated with Franklin (1949).

[2] What, *inter alia*, he might have added can be gauged from the review (Trueta, 1950) which appeared while this account was going to the Press.

[3] According to evidence provided by sections in the Department of Physiology, St. Bartholomew's Hospital Medical College.

The perivenous plexus, in the fœtus, is associated with ? chemoceptive end-organs lying, covered with endothelium, out in the renal vein blood stream, and with ? pressoceptive end-organs which do not so project[1].

The blood pressure in the mature human fœtus *in utero* has only once, so far as I know, been measured and in that instance it was 68 mm.Hg (Haselhorst, 1929). Of hormonal and nervous influences affecting the human pre-natal renal circulation I have no direct evidence, but Govan's (1949) findings in asphyxia neonatorum suggest that, in shock, such blood supply as there is to the kidney is preferentially distributed to the medulla. With regard to urine formation *in utero*, Gersh (1937), on the basis of findings in lower animals, thought that tubular excretory function may begin at 9 weeks in the human fœtus, and resorptive function at 13 weeks, while Morison (1934) stated that urine containing all the standard normal constituents has been found in a fœtus with only three layers of functioning glomeruli. Otherwise fully developed infants, however, have from time to time been born either devoid of kidneys or else without patent urinary passages (Englisch, 1881; Preyer, 1885). So the placenta is competent, if need be, to deal with *all* fœtal fluid excretion, and we can regard the development of the renal circulation and the associated intra-uterine renal performance as graduated exercises which prepare the organ for its post-natal functioning.

At birth the kidney volume is 6·5 ml., and thereafter it rises to reach its final value of 120 ml. at the age of about 16 years (McManus, 1950; *see*, however, Parade, 1926). There is increase in size[2], but not in the total number, of the glomeruli, and, contrary to what obtains in some lower animals, the diameters of the basal and cortical units tend to approximate in course of time; Peter *et al.* (1927) said they were equal at three and a half years. The glomeruli become more spaced out, partly because the cortex increases in size relative to the medulla, partly because the tubular portion enlarges more than the glomerular. Most of the basal glomeruli have flat epithelial covering at four months, but traces of high epithelium persist on cortical glomeruli up to between the fourth and fifth year (Peter *et al.*, 1927). The marked indications of lobulation visible on the surface of the fœtal kidney are smoothed out in post-natal life.

On the functional side, the story is incomplete and its parts inadequately interrelated. It is generally agreed that for the first month or so (*see* e.g. Lasch, 1923; West *et al.*, 1948) the infant's kidney is working relatively imperfectly or immaturely, and with no great reserve against additional stresses. On the basis of surface area, however, the mannitol clearance is normal after the first month, and the adult value for effective renal plasma flow may be reached as early as 30 weeks (West *et al.*, 1948), while urea clearances of children of 2 years and over are the same as those of adults (McIntosh *et al.*, 1928), and children between 4 and 14 years of age gave adult responses to concentration–dilution tests of the Volhard type (Holten, 1931). Figures for blood pressure are very differently given by various authors, e.g. Woodbury, Robinow and Hamilton's (1938) finding of 80/46 mm.Hg in the umbilical artery of a prematurely born 9 months' baby is appreciably higher than many values given for the level at ordinary birth. In general, however, there is agreement about a gradual rise from birth to puberty or somewhat later.

We cannot, from the foregoing evidence, produce any very precise and connected account of the post-natal maturation of the human renal vascular system and circulation, and the only statement (Nash, 1950) suggesting a nervous control of that circulation in its early stages needs some amplification and testing before it can be accepted as evidence. We can, however, believe that at latest by puberty or thereabouts the kidney and its circulatory arrangements are fully developed, in which case we need, to complete this section, knowledge about the length of time during which, in the healthy subject, the state of 100% renal efficiency can continue. The answer is an entirely satisfactory one, namely that it can last, if need be, for so long as a century! For McManus (1950) describes a kidney from a male negro who died in his hundred and fifteenth year, and the organ in question showed nothing abnormal apart from a very few hyaline thickened portions in the glomerular basement membrane. This finding about the kidney as a whole presupposes an adequate renal circulation during the same length of time, and should encourage the clinician in his efforts to prevent departures of that circulation from the normal or, where that is not possible, in his efforts to nullify pathological influences before they have produced irreversible changes.

Anatomy [*Abridged*]

Arteriovenous connexions by-passing glomeruli are of importance in connexion with the

[1]Except for these venous end-organs, the fœtal findings are repeated in the adult.

[2]McManus' figures, lower than those of Külz, are 85 μ for neonatal, and 180 μ to 190 μ, with 200 μ as an outer limit, for adult glomeruli.

interpretation of indirect assessments of renal blood flow and with ideas about the routes taken by the blood in its passage through the kidney. Claims made on behalf of some of the connexions previously listed (Franklin, 1949) need close scrutiny on the quantitative side, while a recent addition to the list (Barrie *et al.*, 1950) is as yet unsupported by adequate published evidence; finally, the experimental findings of Simkin *et al.* (1948) still need the complementary demonstration of the vascular channels involved[1].

The renal lymphatics and renal tissue spaces have been little studied in connexion with the renal circulation in its wider sense. McManus (1950), who makes some mention of them, thinks also that the pyramids and the juxtacortical portion of the medulla must receive extra blood through some non-glomerular channels, but provides no direct evidence.

Measurement of the Renal Blood Flow

Direct determinations of the renal blood flow in animals (e.g. by the use of Rein's Thermostromuhr) have not been beyond criticism, and the methods used are not applicable to man. Certain renal clearance tests, combined with determinations of extraction values, have been introduced with the object of resolving these difficulties. The substances used are excreted, it is supposed, entirely from capillary networks (glomerular and peritubular) and are not reabsorbed; further, extraction is maximal in one passage through the kidney, provided the plasma level is not too high. The extraction value, given as a percentage, is calculated from comparison of arterial and renal venous blood samples (the latter collected in man by means of renal vein catheterization), and is below 100 because, it is believed, a proportion of the total renal blood flow passes through non-capillary channels to reach the renal vein.

The substance first used for such purposes was diodrast (Smith, Goldring and Chasis, 1938), and its use led to the figure of *c.* 1,300 ml. p.m. being given for the renal blood flow in adult man. Subsequently, it was found that sodium para-amino-hippurate (P.A.H.) was treated by the kidney in similar fashion to diodrast, but could be more easily and accurately measured, and had other advantages (Finkelstein, Aliminosa and Smith, 1941; Smith, Finkelstein and Aliminosa, 1945). So it supplanted diodrast. Warren, Brannon and Merrill (1944) were the first to determine its extraction in conjunction with renal vein catheterization in normal unanæsthetized human subjects, and in most of these they found values of 88%[2]. The extraction value in the dog is much the same as in man, but in the *decerebrate* cat it is somewhat lower, namely 75 $\pm$ 3% (Oleesky, 1950, following up the initial work of Black and Saunders, 1949).

If the extraction value does not vary during changes in the total renal blood flow, that is interpreted as meaning that the same *proportion* of the total flow continues to pass through capillary channels. Such constancy was found by Van Slyke (1948) in the dog under various experimental conditions, provided the total flow did not drop to below 3% of its initial value. A drop in the extraction value could theoretically be due to a greater proportion of the total renal flow going through non-capillary by-passes, or to pathological changes occurring in the glomeruli or tubules. The extraction value is found to be low after non-lethal total renal ischæmia of some duration, and the time taken for its complete restoration to normal varies with the length of that ischæmia. The length of time during which animals can stand total renal ischæmia without subsequent death rises from rat (Koletsky and Gustafson, 1947) to rabbit (Scarff and Keele, 1943; Badenoch and Darmady, 1947), and from rabbit to dog (Phillips and Hamilton, 1948). So it is, perhaps, even higher in man.

Other features of intrarenal vascular and circulatory activity, apart from the total blood flow, have been investigated by parallel indirect methods and, even if the findings are not always easy to interpret with certainty, the work as a whole has greatly advanced research upon the activities of the mammalian kidney. Unfortunately, there is not space here for any detailed account of the methods and findings and the deductions made from them—reference must be made to the individual papers.

Nervously- and Hormonally-produced Changes in the Renal Circulation

According to Homer Smith (1943, 56–7), under truly basal conditions no tonic vasomotor impulses pass to the kidney, and the renal blood flow is regulated entirely by the autonomous activity of the renal arterioles. If this view is correct, locally intermediated changes in the

[1]According to Dr. P. M. Daniel (1947; and discussion after this Address), degeneration of basal glomeruli can begin in man as early as the teens, and the direct channels resulting from the process might allow passage of 80 μ spheres. Basal glomeruli constituted about 3% of the total in the kidneys investigated by Xuereb (1948).

[2]In two cases, those with the lowest plasma P.A.H. levels, the values were 100%. In a third case it was zero!

blood flow through part or the whole of the organ could theoretically result from variations superimposed upon this basal state by the action of renal vasodilator and vasoconstrictor nerves. Apart, however, from certain of Bradford's (1889) findings, which require re-investigation and analysis before they can be accepted as evidence of renal vasodilator innervation, the effects of reflex, central, and peripheral stimulation of the renal nerves have invariably, I think, been in the direction of renal vascular constriction and therefore, *ceteris paribus*, of reduction in renal blood flow.

In the mammalian species studied, the renal artery in its extrarenal course can constrict in response to nervous impulses, but I believe that it never does so completely. The evidence upon which my belief is based comes from tracheal occlusion tests, carried out in rabbits after one of the main branches of the artery has been denervated (Franklin, McGee and Ullmann, 1950). Such tests, producing severe asphyxia of the subject, result in maximal nervously-intermediated renal ischæmia and in the cases mentioned, as there was no denervation of the main renal artery, this vessel must have given its maximal constrictor response. Denervation of a branch of this artery results in the portion of the kidney supplied by that branch remaining pervious to blood flow, and under the conditions stated such portion did receive a blood supply, though the still innervated neighbouring portions of cortex, to judge from their marked paling, did not do so. The point is of importance, for some have thought that the nervously-produced constriction of the renal artery, with the consequent distal drop in blood pressure, is sufficient to account for the cortical ischæmia. The experiments mentioned favour the view that the interlobular arteries and their offshoots can constrict completely in response to stimulation which results in only partial constriction of the renal artery.

Nervous effects upon the renal vascular system are not, however, normally as marked as in the tracheal occlusion tests, and we should perhaps consider the theoretically possible results of nervous stimulation upon the intrarenal vessels. These are:

(1) A reduction in all intrarenal calibres leaving *some* blood flow through each glomerulus.

(2) Random intra-cortical shutting down of afferent glomerular vessels.

(3) Progressive occlusion of interlobular arteries and their glomerular branches from the capsular region inwards, the extent of such ischæmia varying with circumstances but being maximal when the supply to the basal glomeruli alone still persists. With only these last representatives of the peripheral vessels still patent, there could be medullary congestion or not according to the degree of reduction of the main renal blood inflow and, in certain conceivable circumstances, of constriction of the renal vein; the site of such congestion would depend on the route or routes used by the remaining renal blood flow in its passage to the renal vein.

(4) Occlusion of all glomeruli and arteriovenous communications, with complete arrest of the renal circulation. In my experience this seems to be beyond the scope of normal nervous influences, though total cessation of flow can be produced by administration of adrenaline in massive dosage.

With regard to (1), (2) and (3) above, I think that (2) is unlikely but that (1) should remain in mind, even though there is no very direct evidence for it, on the grounds that the nervous stimulation so far used has perhaps not included the more delicate degrees, and that urine flow can fall without any marked colour change in the superficial layers of the rabbit's kidney. That (3) occurs under a variety of experimental conditions is beyond dispute, but before giving details may I first briefly consider urine flow in relation to cortical ischæmia? If there is any flow, some glomeruli must be pervious to blood, while anuria can be produced if there is no blood flow to glomeruli, if the effective filtration pressure is too low, or if reabsorption is complete. Increased urine flow can occur as the result of increased blood flow, increased effective filtration pressure, and decreased reabsorption. Urine flow determinations can, therefore, be of help in assessing circulatory changes, though their interpretation may on occasion be difficult. In the Oxford studies of the renal circulation, this and certain other possible aids were not invoked, but they are now being called into service.

Reverting now to the renal blood flow, I wish to state that our demonstration of the possibility of the complete exclusion of cortical glomeruli from the circulation, with more and more layers becoming affected, from the capsule inwards, as the stimulation increases in intensity and/or duration until finally only the basal glomeruli remain pervious, was perhaps *the* novel addition to knowledge made through the researches of the Oxford team from 1945 onwards. For this pattern of effect,[1] with its apparent parallels in renal pathology, was not

[1]Seen first as the result of nerve stimulation, but later obtained also with hormones and other chemical substances.

appreciated before February 1946, when Dr. Trueta gave a résumé of our findings to date to a small group of medical visitors. The renal artery being simultaneously reduced in cross-sectional area, the blood of which the cortex is deprived is, for the most part, re-routed to other parts of the body and does not reach the kidney at all. If, however, the total renal inflow falls by less than the amount which the cortex loses, more blood passes through the routes still remaining open to reach the renal vein, and these routes theoretically include not only the basal glomeruli-vasa recta pathways, but also any other arteriovenous communications, unassociated with glomeruli, that may be available—hence my reference to these in the section on anatomy, So there may be hyperæmia in the cortico-medullary junctional zone and/or elsewhere in the medulla. On the other hand, the medulla can, on occasion, be paler than normal (this is so in the film which I shall project), in which case the drop in total renal blood flow has presumably been greater than the amount of which the cortex has been deprived. In the absence of definite evidence of the function of the residual blood flow on its way to the renal vein, and in view of the small proportion of the total resting flow which it represents, it may be somewhat academic to devote too much attention to it, and I have only devoted this much in order to clarify some of the points in Trueta *et al.* (1947).[1] To conclude this mention of the cortical blood flow diversion, I should add that the intrarenal circuit time may be reduced by as much as 40% during its occurrence ; that the blood in the renal vein may become partially or wholly arterial-red in colour and that more rarely the flow may be pulsatile ; that there may be a retrograde passage of blood from arcuate to interlobular veins and ? tubular capillaries, but not right back to the cortical glomeruli ; finally, that the diversion pattern found first in the rabbit has been noted also in the rat, mouse, cat, dog, and (Scott) monkey, i.e. in all the mammals so far investigated. It is, therefore, possible that nervously-intermediated departures from the normal level of renal blood flow in man, are, on occasion, accompanied by similar exclusion of cortical glomeruli from the circulation ; that, conversely, reported rises in the blood flow may have meant re-inclusion of such glomeruli within the circulation.

The nervous regulation of the renal blood flow is mediated through centres in the central nervous system, diverse afferent pathways to those centres, and sympathetic efferent pathways terminating in the renal nerves. Evidence that spinal centres exist in some animals has been obtained in asphyxia studies (Franklin, McGee and Ullmann, 1950), and centres in the brain are in course of being identified, particularly by E. C. Hoff and his colleagues in the University of Virginia. They found (1949) in cats that excitation of the pressor area (foci on gyrus proreus, gyrus sigmoideus, and orbital and mesial surfaces of the cerebral cortex) resulted in bilateral renal cortical ischæmia, provided the renal nerves were intact. Twelve years earlier Green and Hoff (1937) had reported diminution in volume of the innervated, but increase in volume in the denervated, kidneys of the cat *and the monkey* during pressor responses evoked by electrical stimulation of the cerebral cortex. The more recent work is still proceeding, but I do not think I am justified in adding later information, contained in personal letters, about the results obtained in that and in certain other laboratories.

Afferent pathways to the renal vasomotor centres are numerous. They are present, for instance, in the sciatic nerve, and also in nerves supplying the uterus, intestine, bladder, ureter, and—I suspect—the kidney itself. In the cases of the hollow viscera, an adequate stimulus seems to be sudden distension, especially when combined with indisposition on the part of the smooth muscle to relax. Professor Amoroso has encountered some striking examples in respect of the animal uterus, and I have been told of a human case in which an attempt to induce labour by increasing the uterine distension resulted in acute bilateral cortical necrosis. Direct stimulation of spinal or higher centres by oxygen lack or carbon dioxide excess, or perhaps reflex effects from the kidney via these centres, seem to account for the effects of asphyxia upon the renal circulation (*see* Film Details p. 474).

In our work at Oxford during 1945 to 1947 we noted a tendency for the vessels of the hind-limbs and abdomen to be constricted preferentially in the order femoral artery, abdominal aorta, renal artery, and mesenteric artery—this last might even dilate. This, and further findings led me to the idea of an " order of sacrifice ", which I tested out, in conjunction with Professor Amoroso, by determining the differential reactivity of various arteries to massive doses of adrenaline, injected into the general circulation. Briefly, if such reactivity to adrenaline is

[1]While speaking of this part of our work, may I deal with two other matters? The first is that I personally have never liked the terms "greater circulation" or "lesser circulation" of the kidney, and that I find my overall mental picture of the renal blood flow and its variations the better for their exclusion. The second is that, *in the absence of a precise definition*, I deprecate the use, as much as I appreciate the brevity, of the term "renal shunt" or "Oxford shunt". With a precise, agreed connotation the term would be of great service.

a guide, the skin, limb musculature, renal cortex, gut, brain, and heart, are likely to be sacrificed in that order as the circulation progressively fails. The full story is not ready for publication and I mention these points here partly because they suggest the relative importance of the renal cortical blood flow in the circulatory economy, partly because they explain, I think, the success achieved by Dr. Hingson (1949) in a certain therapeutic use of ephedrine.

The possibility that the afferent and efferent glomerular vessels are not equally affected by adrenaline has often been discussed since the paper by Richards and Plant (1922) appeared, and Homer Smith (1943) interpreted indirect evidence as favouring the view that the efferent vessels are the more sensitive. I have, however, heard at least one alternative explanation and I would not regard the matter as by any means finally settled. Another point in the adrenaline story is unequivocal, namely, that the acutely denervated kidney reacts more rapidly, more intensely, and for a longer time to the hormone than does the innervated kidney (Hartmann *et al.*, 1937 ; Franklin, McGee and Ullmann, unpublished) ; this is very noticeable in the film which I shall project after my lecture.

The other naturally occurring product of particular interest is the antidiuretic hormone of the neurohypophysis. As the result of the work of Verney (*see* Verney 1947, 1948) and of many others, the story of its release in emotional stress and short-lived exercise, through osmotic changes in the blood going to the brain, and in response to injection of acetylcholine or nicotine or to the smoking of cigarettes in unduly trying ways, is well known. What are not yet equally well known are the effect, if any, which it has upon the intrarenal circulation, and the relation of this to the antidiuretic action. The inhibition of water diuresis by emotional stress is independent of the renal innervation, is not caused by endogenous release of adrenaline, is unaccompanied by any appreciable change in the total blood flow through the kidney, and comes on within a relatively short time—some 2 mins.—after the application of the stimulus (Verney, 1948). In appropriate concentrations pituitrin and pitressin can produce paling of the rabbit's and particularly of the rat's kidney surface with little apparent effect upon the calibres of the main renal artery and vein (Trueta *et al.*, 1947), which suggests that any marked action that these hormones may exhibit must be upon structures within the organ. But the experiments which produced these findings need to be extended, and we cannot at present state either fully or precisely what are the renal circulatory actions of posterior pituitary secretion, and of its individual constituents, under physiological conditions. One of the latest discussions of some aspects of the problem is that given by Koella (1949).

Some Questions and Attempts at Answers

The recounting of the effects of nervous and hormonal influences upon the mammalian renal blood flow suggests a variety of questions, such as :

(1) Under what natural conditions may a partial or complete diversion of the renal cortical blood flow occur in man ?

(2) How does it affect kidney functions ?

(3) For how long can it exist without irreversible changes occurring ?

(4) What are these irreversible changes when they do occur ?

(1) Among the natural conditions in which the diversion may perhaps occur are :

(*a*) *Exercise.*—White and Rolf (1948) showed that the " effective " renal plasma flow is reduced and that, in severe exercise, not only may the reduction be as great as 80%, but there may be proteinuria as recovery takes place. This suggests, they stated, though it does not prove, that in strenuous exercise many glomeruli may have their blood supply interrupted, the subsequent proteinuria being due to the reversible temporary damage undergone by these glomeruli during their exclusion from the blood circulation. Rise in plasma glucose, ? an index of increased adrenaline output, was observed when the exercise reached a high level.

(*b*) *Abnormal pregnancy.*—Odell (1947) found reduction in inulin, exogenous creatinine, and urea clearance rates in severe pre-eclampsia, with improvement during the puerperium. " Severe cases ", he added, " cannot be accurately investigated by the usual clearance methods employing collected urine specimens. Consequently, additional evidence is necessary to determine the exact mechanism of oliguria and anuria. The possible etiologic significance of angiospasm is postulated." Very recently Kenney, Lawrence and Miller (1950) have found that in normal pregnancy the afferent glomerular resistance is raised to a minor degree, the glomerular pressure is reduced, and the filtration rate remains normal. In " toxæmia of

late pregnancy ", on the other hand, the renal plasma flow is reduced, the afferent arteriole is constricted, and there are falls in glomerular pressure and filtration rate. In some cases compensation in the way of efferent constriction tends to restore the glomerular pressure to a more nearly normal value. To this evidence, which suggests to the authors *either* a reduction in the blood flow per unit mass, *or* no change in this but a reduction of the total mass, we can add findings such as that of Solymoss (1949), who correlated pre-mortal anuria of an eclamptic patient with cortical pallor and medullary congestion seen in the kidney at autopsy. We have already mentioned acute bilateral cortical necrosis produced by sudden uterine distension. On the whole it looks very possible that diversion of renal cortical blood flow may occur abnormally in human pregnancy, but the case is not, of course, proven.

(*c*) *Severe asphyxia.*—The results found in animals (Franklin, 1948 ; Franklin, McGee and Ullmann, 1949, 1950) suggest that severe anoxia, produced by carbon monoxide poisoning or by a low percentage of oxygen in the inspired air, may reduce the renal cortical blood flow in man, and in this connexion Bradley and Bradley's (1947) paper is not without interest.

(*d*) ? *Acute rapid hæmorrhage*, but not gradual hæmorrhage. This again is a suggestion from results of animal experiments (Trueta *et al.*, 1947 ; Van Slyke, 1948). Van Slyke, using clearance tests in dogs, found that a preferential restoration of the renal blood flow soon followed, unless hæmorrhage had been excessive. He postulated production of V.E.M., as described by Shorr, Zweifach and Chambers, to account for the full recovery, and of V.D.M. to explain the decline, after some measure of recovery, which followed too severe a loss.

Apart from the above conditions, rarer ones such as dioxan poisoning rise to mind. Dioxan has caused acute cortical necrosis in man (Barber, 1934) and tubular necrosis in animals (De Navasquez, 1936), and it can certainly produce renal pallor in rabbits, though the exact mechanism remains to be elucidated (Franklin and Sophian, unpublished).[1]

(2) How the diversion affects kidney function must be considered under two headings, namely, what happens in the still aerobic part of the organ, and what happens in that part which is rendered ischæmic by the diversion. With regard to the former problem, the answer must depend on

(*a*) Whether the reduction in total renal inflow corresponds with the reduction in number of glomeruli, i.e. on whether or not a different proportion of the renal blood flow traverses arteriovenous channels which are unconcerned with the process of urine formation.

(*b*) Changes, if any, in glomerular filtration pressure and other factors.

The functions of the temporarily anoxic portion of the kidney are of interest and, if diversion is at all frequent in normal life, of importance. For such renal tissue is the sole known site of production of V.E.M., which is one of two factors that in large measure control the peripheral circulation, in the body generally, distal to the arterioles (*see* Shorr *et al.*). It increases the frequency and amplitude of the constrictor activity (vasomotion) of the metarterioles and precapillary sphincters, and very greatly enhances their reactivity to the topical application of adrenaline. It is inactivated by the kidney tissue when the latter's oxygen supply is restored. The ischæmic kidney also liberates renin, which acts upon a plasma globulin, hypertensinogen, to produce hypertensin, which raises the blood pressure. The enzyme, hypertensinase, which inactivates hypertensin, is yet another product of the kidney. All together, then, this organ has a multifarious connexion with the regulation of the blood circulation, and there is a considerable interdependence between local and general blood flow arrangements.

The residual blood flow which still passes through the kidney during maximal exclusion of cortical glomeruli may have a maintenance function, including prevention of any serious change in temperature of the organ. But about this there is no evidence, merely ideas about possibilities.

(3) and (4) The third question, "How long can cortical diversion exist without irreversible changes occurring?" is not easy to answer precisely. Hamilton, Phillips, and Hiller

[1]Barium sulphide, used to depilate rabbits, can produce cortical blood flow diversion (Amoroso, Trueta and Franklin, unpublished). More information about the actions of nephrotoxic drugs is being accumulated through the researches of Dr. J. E. Cotes, but I will not anticipate any part of his story, or assess the applicability of his findings to man.

(1948) found in dogs that clamping the left renal artery, after the right kidney had been removed, resulted in death in uræmia if the period of clamping exceeded four hours. Further experiments, by Phillips and Hamilton (1948), showed that renal blood flow was rapidly resumed at a nearly normal rate after twenty minutes to two hours of ischæmia. Clamping the renal artery, however, is a more drastic procedure than producing a diversion of the cortical blood flow, and the only suggestions I have about the length of time during which the latter can be continued without irreversible changes occurring come from some very preliminary experiments carried out by Mr. Sophian and myself. From these it appears that about four hours of continuous diversion, produced by stimulating the renal nerves for thirty seconds every two minutes, may be more than the rabbit's kidney can stand. In one instance, however, there was diminution in extent of a superficial area, visibly affected by the stimulation, during a subsequent recovery period of a few hours' duration. Effects which have been produced by such stimulation have included, according to reports by Professor J. H. Dible and Dr. G. J. Cunningham, localized cortical necrosis, and elsewhere very considerable tissue damage. The results to date are, thus, encouraging but much more obviously remains to be done before any adequate and incontestable story can become available. A point of interest in one experiment was that the unstimulated kidney showed superficial paling during the recovery of the stimulated one.

Summarizing Remarks

From all the information available, it is possible to build up a fair mental picture of the fully developed mammalian renal blood flow and of its variations. In most of the circumstances of everyday life it represents a considerable part of the total cardiac output, and the changes which it exhibits are effected, in so far as the kidney is concerned, through small or moderate adjustments, falling far short of complete occlusion of any vessels, in the degree of vascular constriction. Beyond this routine range of variability more marked falls in intrarenal blood flow can occur in consequence of more serious nervous or chemical action upon the vascular apparatus. There appear to be two main patterns. In the first one, the afferent and/or efferent glomerular vessels are constricted to an extent incompatible with full physiological efficiency of the tubules and (in the case of afferent vascular constriction) of the glomeruli. In the second one, there is actual diversion, in part or in whole, of the blood supply that would normally go to the cortical glomeruli ; with the maximal number of glomerular layers rendered ischæmic, the residual renal blood flow is very small, but it is probably never nil in the absence of general circulatory failure. The more marked changes which I have mentioned probably occur over comparatively short periods as part of the full *physiological* picture, for animals are not always anæsthetized or human beings always under basal conditions, and demands upon the body's reserves of reactivity are, on occasion, maximal. The changes become, on the other hand, part of the *pathological* picture when they continue too markedly for too long a time, and they can result in death when the bounds of recovery possibilities have been overstepped. Short of a fatal outcome, they may leave the kidney functionally less perfect and/or structurally scarred.

Acknowledgments

In the preparation of this paper I have received considerable help from various members of my Staff, particularly Miss E. A. Ullmann and Dr. A. M. Miles ; I have also received several useful suggestions from Mr. G. J. Sophian. To them all I express my thanks.

Film Details

The colour film, photographed by Mr. Douglas Fisher, which was projected after the address consisted of the following parts :

(1) Red stream lines in the renal vein.

(2) Anoxic diversion of the renal cortical blood flow.

Part I (K. J. Franklin, 1948). Part II (E. Ullmann, L. E. McGee, and K. J. Franklin, 1949).

(3) Effects of anoxia and of adrenaline respectively upn the innervated and the denervated kidney.

(4) Excretion of myoglobin by the kidney.

The second item was projected by courtesy of Blackwell Scientific Publications Ltd., the others by courtesy of the Wellcome Foundation Ltd. The subjects used in all four items were anæsthetized rabbits.

POSTSCRIPT

After the lecture and film-projection, Professor T. N. A. Jeffcoate told me of an obstetric case in his recent experience, and very kindly gave me permission to give some account of it here. The patient had concealed accidental hæmorrhage, and anuria from the time of its onset. After twenty-eight hours, when she had recovered from the initial shock, looked well, and had a blood pressure within normal limits, she was operated on and one kidney was exposed. Superficially it did not look pale, but congested. The pedicle was completely denervated without any change becoming apparent on the kidney surface and, when incised, the capsule did not bleed at all, nor did the cortex. On the other hand, so soon as the medulla was reached there was bleeding. The patient died on the tenth day after delivery, and at autopsy both kidneys showed the classical picture of complete cortical necrosis.

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Clinical Section

President—W. A. BOURNE, M.D.

[*January* 13, 1950]

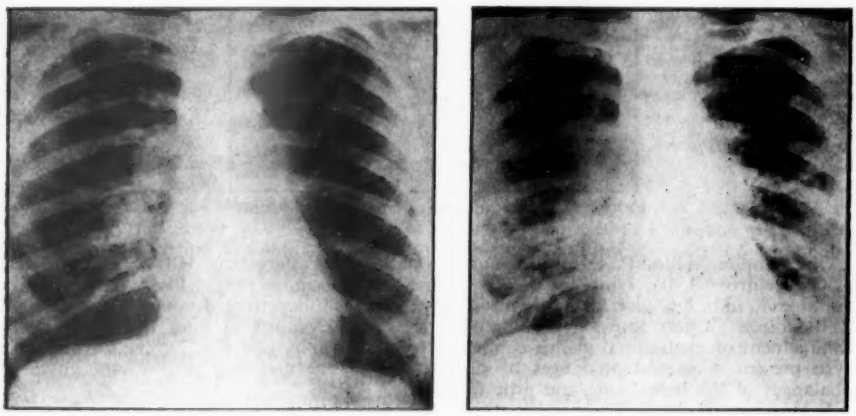
Two Cases of Sarcoidosis of the Lungs with Erythema Nodosum.—O. GARROD, M.D.

I. Mrs. R. S., aged 29, housewife (ex-hospital nurse). (Shown by permission of NEVILLE OSWALD, F.R.C.P.)

Diagnoses.—(*a*) Sarcoidosis of lungs and lacrimal glands. (*b*) Migraine. (*c*) Erythema nodosum.

History.—Quite well until nine months ago when she had an attack of left hemianopia followed within half an hour by numbness of left hand and face for a quarter of an hour, then by severe frontal headache lasting for half an hour. She felt dizzy for several days afterwards. During the following month she had three similar attacks, then a fourth attack in which the hemianopia was to the right.

Six months ago: Typical erythema nodosum of legs and later of arms lasting about a month and accompanied by fever and pain in the knees, elbows and wrists. Since then, she has felt tired and run down.



A.—At time of erythema nodosum. B.—Six months later.

FIG. 1.—Case I.

Five weeks ago: Developed a slight cough and sputum.

One week ago: Noticed slight puffiness of upper eyelids. Has not lost weight.

Annual chest X-rays and Mantoux tests were done from 1939 to 1941 by the Prophit Survey:

Four chest X-rays all negative.

Mantoux tests (1 : 10,000 O.T.)—June 1938: +++ reaction 20 mm. in diameter. April 1939: + reaction, 5 mm. in diameter. August 1940: ++ reaction, 10 mm. in diameter.

On examination (December 1949).—Healthy-looking patient with slight prominence of lateral half of both upper eyelids beneath which the lacrimal glands are distinctly palpable. No other physical signs.

Whilst in hospital she had an occasional evening pyrexia of 99°.

Investigations.—E.S.R. 14 mm. Blood count: R.B.C. 3,900,000; Hb 86%; W.B.C. 6,000 (normal differential). Serum proteins: total 8 grammes % (alb. 5, glob. 3). Sputa Ziehl-Neelsen negative. Radiographs: Skull, hands and feet normal. Chest: In April 1949 (at time of erythema nodosum, Fig. 1A) bilateral hilar gland enlargement. Later films show diffuse mottling compatible with pulmonary sarcoidosis (Fig. 1B). Mantoux test negative to 1 : 100. Lumbar puncture: Pressure and Queckenstedt normal; protein 75 mg.%; globulin faint +; cells less than 2. W.R. and Lange negative. E.E.G.: No significant abnormality noted.

Ophthalmic examination reveals some myopia but no other sign of intra-ocular disease.

II. Miss E. K., aged 51; State-registered nurse. (Shown by permission of A. W. SPENCE, M.D.)

Diagnoses.—(*a*) Sarcoidosis of lungs and phalanges. (*b*) Erythema nodosum.

History (August 1949).—Quite well until five months ago when she noticed a large, raised, tender, bluish-red swelling in the right thigh which lasted for about three months. Since then, numerous similar lesions, from half an inch to three inches in diameter, have appeared on both legs and thighs. For a few months she has noticed increasing breathlessness.

On examination (August 1949).—About seven typical lesions of erythema nodosum were present on the flexor and extensor surfaces of the legs and on the thighs. There were also a few small infiltrated plaques resembling sarcoid lesions on the backs of the legs and on the thighs.

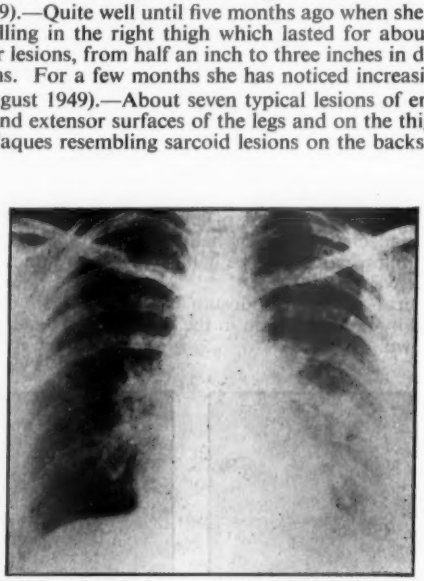


FIG. 2.—Case II at time of erythema nodosum.

Investigations.—Blood: E.S.R. 25 mm. in one hour (Westergren). Hb 102%; W.B.C. 5,500 (neutros. 3,905, lymphos. 1,320, monos. 110, eosinos. 165). Plasma proteins 7 grammes% (alb. 5·6, glob. 1·4). Mantoux test: 1 : 1,000 negative; 1 : 100 weak positive. Radiographs: Chest shows typical appearances of sarcoidosis in both lung fields and enlargement of mediastinal glands confirmed by tomography (*see* Fig. 2). Hands: Small cysts present in second phalanges of right index, middle and ring fingers, and in first phalanges of left index, ring and little fingers.

Subsequent progress.—The erythema nodosum subsided two months after she attended hospital. She has remained well apart from some breathlessness. No treatment has been given.

Chronic Lymphatic Leukæmia with Hæmolytic Anæmia. Splenectomy.—M. S. R. HUTT, M.D., M.R.C.P. (for J. S. RICHARDSON, M.V.O., M.D.).

Mrs. A. P., aged 60, first attended hospital in April 1948 with a bad attack of pharyngitis. Routine examination revealed slight enlargement of the spleen.

Blood count.—R.B.C. 4,500,000; Hb 80%; W.B.C. 22,300 (polys. 55, lymphos. 43, monos. 1, eosinos. 1%).

Diagnosis.—Early case of lymphatic leukæmia. Patient was kept under observation

March 1949: Dragging pain in the abdomen, weakness and tiredness. Examination now revealed marked splenomegaly and enlarged glands in the left axilla. She appeared to be slightly icteric.

First admission.—29.3.49: R.B.C. 3,600,000; Hb 66%; W.B.C. 53,000 (polys. 16, lymphos. 77, monos. 4, eosinos. 1, basos. 1, transitional myelos. 1%).

13.4.49: R.B.C. 2,300,000; Hb 45%; W.B.C. 29,000 (polys. 11, lymphos. 89%).

Sternal marrow showed 73% of lymphocytes, confirming the diagnosis of lymphatic leukæmia.

15.4.49: Blood transfusion (3 pints).

20.4.49: Radiotherapy started.

28.4.49: Patient definitely icteric. Icteric index: 16. Urine contains excess of urobilinogen. Race-Coombs test positive. Blood transfusion (3 pints).

29.4.49: R.B.C. 3,000,000; Hb 66%; W.B.C. 13,200 (polys. 23%, lymphos. 72%). Radiotherapy stopped in view of fall in white count. Discharged. Clinically slight improvement. Anicteric.
13.6.49: Hb 90%.
4.7.49: Seen in follow-up clinic complaining of increasing dyspnœa and tiredness. Clinically anæmic and icteric. Readmitted. Hb 53%.
6.7.49: Transfusion (cells from 4 bottles).
9.7.49: Hb 62%.
10.7.49: Icterus deeper. Urine contains excess urobilinogen.
13.7.49: Hb 48%; W.B.C. 53,700 (polys. 22%).
15.7.49: Transfusion (cells from 4 bottles).
18.7.49: Hb 49%; retics. 12%; fæcal urobilinogen 2,900 mg.
21.7.49: Transfusion (cells from 8 bottles).
24.7.49: Hb 88%.
27.7.49: Splenectomy carried out.
4.8.49: R.B.C. 4,500,000; Hb 78%; W.B.C. 30,000 (polys. 24%, lymphos. 71%).
24.8.49: R.B.C. 4,500,000; Hb 82%; W.B.C. 29,000 (polys. 9%, lymphos. 87%). Discharged, symptom free.
24.10.49: Seen in follow-up clinic. Feels very fit. Blood count: R.B.C. 5,000,000; Hb 108%; W.B.C. 26,000 (polys. 21%, lymphos. 75%).
21.11.49: R.B.C. 5,100,000; Hb 102%; W.B.C. 20,000 (polys. 35%, lymphos. 58%).

Erythromelalgia in One Lower Limb.—GERALD SLOT, M.D.

V. S., female, single, aged 46, complained of pain of the lumbago kind, in the back of her leg.

Prolapsed disc was diagnosed and she was operated on in June 1948 by Mr. E. H. T. Hambly when an inflamed fifth lumbar spinal nerve root on the left side was found.

Investigations by Mr. J. B. Kinmonth at St. Bartholomew's Hospital: Angiograms showed there was no organic obliteration in either the arteries or veins and the symptoms of the foot were of the spastic type.

The pain continued and the question of a lumbar ganglionectomy was considered. Dr. J. Aldren Turner found no evidence of a root lesion and considered that some psychiatric treatment would help. The patient attended a Psychiatric Department once but did not continue. Since then she has been manipulated twice but still complains of pains at the bottom of her back and down the left leg, and blueness of the left foot.

Blood count (1.11.49).—R.B.C. 5,100,000; Hb 100%; C.I. 0·98; W.B.C. 6,000 (neutros. 57, basos. 1, lymphos. 39, monos. 3%).

B.S.R. (Wintrobe) 1st hour 13 mm., 2nd hour 30 mm.

X-rays of back and pelvis negative.

There is some sensory loss over the lower part of the left leg and the left knee-jerk is diminished. Lower limb is blue and colour increases as does pain in dependent position. Pulses of foot are felt.

The diagnosis is between erythromelalgia or ischæmia and suggestions for treatment are invited as her pain has so far resisted all forms of therapy.

POSTSCRIPT.—She has since had a sympathectomy and this has helped considerably.

Dr. A. C. Dornhorst: The outstanding feature of this foot is that the skin flow is much reduced. This can be demonstrated by emptying the veins and then seeing how long they take to refill while gentle constriction is applied proximally. The arterioles must therefore be either occluded or constricted and it is the venules that are dilated and which give the high colour. I do not think the term "Erythromelalgia" should be applied to this condition. If in this case the dorsalis pedis artery were impalpable one would have no hesitation in saying that it is a typical ischæmic foot with "rest pain". However, since the dorsalis pedis pulse is full, the smaller distal vessels must be either occluded or in spasm. As far as I can make out the history is not at all episodic and I think this makes spasm very unlikely. I think it is, therefore, ischæmia due to obstruction of the small distal vessels.

Dr. F. Parkes Weber considered that, whatever the exact ætiology might be, the case could be termed "chronic erythromelalgia of one lower limb". Acute cases might completely subside with or without special treatment. He remembered the complete disappearance of the erythromelalgic symptoms in an acute case. The patient (a woman) was found to have splenomegalic polycythæmia of the Vaquez-Osler type and was under observation till shortly before she left England. There was no recurrence of the erythromelalgia, which had been limited to one lower limb. A rare condition of one-sided red turgid hand in young women appeared to be partly of psychoneurotic origin.

Arteriosclerosis. Thrombosis of Iliac Arteries.—J. B. KINMONTH, M.S., F.R.C.S.

G. H., male, aged 50; a plumber.

History.—Twelve years' intermittent claudication in both calves, gradually becoming worse.

The right leg is worse than the left and has almost continuous rest pain with numbness and coldness in the foot.

State on admission in December 1949.—Erythrocyanosis of right foot which was colder than the left. Moderate postural colour changes in right foot. Pulses absent below the femoral artery on both sides.

Straight X-ray.—Calcification in anterior and posterior tibial arteries of both sides.



FIG. 1.

Aortography (January 3, 1950. General anæsthesia).—This outlined the arterial tree from the abdominal aorta downwards into the thighs and is herewith reproduced (Fig. 1). The chief points of interest are the block in the right external iliac extending as far as the common femoral the faint outline of which, filled by collaterals, is just discernible on close examination. The right internal iliac artery and branches are well filled.

On the left side the external iliac is patent and well filled with dye but the internal iliac is not to be seen and at its expected point of origin from the common iliac there is a well-marked notch presumably due to thrombosis.

Operation (January 7, 1950).—Thoraco-lumbar sympathectomy.

Progress after operation.—Forty-eight hours after operation measurements of the blood flow in the right leg during reactive hyperæmia (Dr. Dornhorst) showed it to be twice the pre-operative rate.

The rest pain in the right leg and foot has been relieved.

Comment.—Angiography showed, as no other method could, the high level of the obstruction and the need for a sympathectomy extending somewhat higher than the routine lumbar one if the collaterals around the blocked segment were to be denervated.

Elephantiasis of Left Lower Limb.—JOHN F. R. BENTLEY, F.R.C.S.

Mr. H. first came under observation in September 1942, when he complained of swelling and aching in the left ankle of gradual onset over the past one and a half years. He gave no history of previous trauma or relevant disease. There was no family history of elephantiasis.

On examination.—The only abnormalities detected were: (1) Pitting œdema of the left ankle; (2) swelling of the left inguinal glands; (3) the presence of a button-like disc 1 cm. in diameter, brownish-purple in colour, with a scaling centre situated on the back of the left calf. This had been first noticed at the age of 10 years.

The skin lesion was excised for histological examination.

Report.—"The 'tumour' shows only a subepithelial immature cellular connective tissue with scanty lymphocytic infiltration. There is no evidence of a specific inflammatory cell exudation or reaction. The surface epithelium is a regular normal cell layer."



FIG. 1.

At a later date the swelling of the ankle spread upwards to involve the rest of the leg and thigh, there being transient exacerbations and remissions. During this period investigations included full blood count, which was essentially normal, and W.R. and Kahn tests which were negative. In the middle of 1943 the enlarged inguinal glands were excised with the hope of removing an inflammatory focus that might be aggravating the condition.

Operation notes.—"Vertical inguinal incision. Flat mass of fibrous tissue almost replaces the inguinal glands and thick trunks of fibrous tissue (? lymphatic channels) pass off down the leg, a few deeply and upwards, and some laterally."

Histological report on specimen.—"Sections from this tissue represent the results of some inflammatory lesion resulting in extensive lymphatic gland fibrosis with sclerotic changes in lymph cords and companion vessels. Only occasional collections of lymphoid cells remain in the glands, the normal architecture being completely destroyed. No sign of germ centres now remain, nor is there evidence of the former gland reticulum. Aerobic and anaerobic cultures do not yield any growth."

Up to the present date the leg has continued to increase in size without beneficial effects from elevation, elastic stockings or massage. Radiographs of the two lower limbs in November 1949 show no difference in the size of the bones or changes in the bony structure. During the past week Frei-Hoffmann test has been negative.

The present condition is seen in Fig 1. The swelling is solid except for the foot where it pits on pressure. It is not distributed evenly, but shows excrescences which do not correspond with any anatomical structures. The toes are not œdematous or enlarged.

The weight of the limb is proving a considerable burden and the question of amputation or a plastic excision of subcutaneous tissue is being considered.

Dr. F. Parkes Weber agreed that the case was one of non-tropical elephantiasis of one lower limb, but he did not think it was of neurofibromatous origin. There was no real evidence of any neurofibromatosis. Even if the small superficial lesion which had been excised from the back of the leg was a molluscous fibroma, its presence was no proof that the patient had neurofibromatosis. It had existed in a stationary condition from early life; probably one in about every two hundred persons had one or two small molluscous fibromata from childhood, without having "neurofibromatosis". He (Dr. Weber) said that he regarded the case as one of chronic progressive lymphatic (? fibrotic) obstruction of the affected extremity, which had to be termed "idiopathic". It perhaps might be suggested that the mass-excision of lymphatic glands from the left groin had accelerated the elephantiasic swelling of the limb.

Malignant Mediastinal Teratoma.—F. V. GARDNER, M.D.

P. A., male aged 30. May 1949: Attended a chest clinic complaining of a single small hæmoptysis. A.P. and lateral teleradiograms normal. 17.8.49: Admitted to the Royal Free

Hospital complaining of five weeks' continuous dull substernal pain and dyspnœa on exertion.

On examination.—Irregular fever to 100°; pulse 90–120; expansile pulsation visible over left upper chest; large pericardial effusion with partial left lower lobe collapse. No lymphadenopathy.

Investigations.—Teleradiograms (Figs. 1 and 2) showed large pericardial effusion and a rounded mass lying in the anterior mediastinum and extending outwards into the left upper zone.

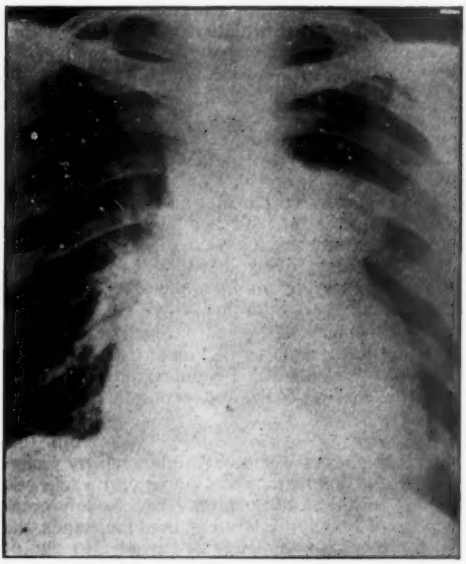


FIG. 1.—Teleradiogram.—A.P. (17.8.49) showing pericardial effusion and rounded mass extending into the left upper zone.



FIG. 2.—Teleradiogram left lateral (17.8.49) showing mass in the upper anterior mediastinum.

Hb 75%; W.B.C. 8,300, normal differential. E.S.R. 27 mm. W.R. negative. Pericardial fluid: straw-coloured, 600 cells/c.mm. 56% polymorphs, 44% lymphocytes; also degenerate cells with large and deeply staining nuclei, suspicious but not diagnostic of malignancy. Bronchoscopy showed nothing abnormal.

Treatment.—Full course of deep X-ray therapy to mediastinum.

Course.—Fever, anæmia and pericardial effusion increased during radiotherapy and congestive cardiac failure developed; no significant decrease in size of tumour mass. Thereafter paracentesis of the pericardium, blood transfusions and general measures improved the local and general condition and the cardiac failure and pericardial effusion disappeared. The mediastinal mass, however, increased in size. Teleradiogram 10.11.49 (Fig. 3) showed no pericardial effusion; the mass seen in the earlier films was larger and below it was an irregular rounded mass extending outwards from the left border of the heart. 16.11.49: Thoracotomy: a large vascular necrotic tumour was found situated in the anterior mediastinum and extending into the left upper lobe. Biopsy report: malignant teratoma. Thereafter the patient's condition deteriorated rapidly and he died on 12.12.49.

Autopsy (Dr. A. G. Stansfeld).—A massive tumour arising in the upper anterior mediastinum extended from the thoracic inlet above to the diaphragm below, enveloped the whole anterior aspect of the heart and reached the lateral chest wall on the left side, causing collapse of the left lung from pressure. Hæmorrhagic metastases in both lobes of the liver. Testes normal. Histology: Malignant teratoma, primary growth and liver metastases showed mixed epithelial and mesenchymal components.



FIG. 3.—Teleradiogram.—A.P. (10.11.49) showing no pericardial effusion; the rounded mass is larger and there is an irregular mass below it continuous with the heart shadow and extending into the left lung field.

Comment.—The extensive pulsation of the upper left chest was an unusual feature and was presumably transmitted pulsation due to the attachment of the tumour to the great vessels. The position of the tumour and the lack of response to radiotherapy made the diagnosis of malignant teratoma most probable in spite of the entirely normal teleradiogram only three months before admission.

Lymphosarcoma of Cheek.—H. A. KIDD, F.R.C.S.Ed.

Girl, aged 12.

At the beginning of November 1949 she developed a swelling inside her left cheek, which was a little painful and interfered with her eating. The doctor treated her with penicillin but the tumour enlarged. She attended the Casualty Department where the lower molar was extracted for caries and ? apical abscess. On 24.12.49 the tumour was aspirated and incised and some thick pus said to have been obtained.

She was referred to the outpatient department and was then seen to have a swelling in the left cheek which was not attached to either upper or lower jaw. She was admitted to hospital that day.

On admission there was some adenitis on the left side of the neck, the glands being small and soft. There was considerable trismus and an X-ray of the antrum showed mucocele in left antrum along lateral wall in particular; the lateral wall showed unerupted wisdom in high position. Swab from ulcer: "Numerous Gram-negative bacilli. Few Gram-negative diplococci and Gram-positive cocci. Cultures (aerobic-anaerobic). Mixed growth of *N. catarrhalis*, diphtheroids and non-hæmolytic streps." Intermittent pyrexia not exceeding 100° at night. The condition was thought to be either actinomycosis or a sarcoma arising primarily from the cheek (Fig. 2).

3.1.50: A large fleshy tumour was exposed and a biopsy performed. Section report: "Acutely inflamed granulation tissue. Condition may be actinomycosis but no positive sign of this was seen. No evidence of malignancy seen."

Treatment with penicillin and streptomycin for twelve days, but the tumour continued to enlarge rapidly.

8.1.50: Biopsy aspiration of tumour which was still enlarging rapidly. Pathological report on film: "*Slides. Thinner film*: numerous R.B.C. and round cells resembling primitive lymphocytes. Almost certainly neoplasm. Malignancy cannot be excluded. *Thicker film*: Mainly R.B.C. with a smaller number of polymorphs, a few lymphocytes and an occasional larger round cell. *Material in saline*: Gram: No organisms seen. Aerobic culture, Anaerobic culture: both sterile."

Diagnosis of lymphosarcoma was made and patient transferred to the Royal Cancer Hospital for radiotherapy.

POSTSCRIPT.—Radiotherapy was given at the Royal Cancer Hospital, the patient receiving the following treatment:

January 17 to 26: H.V.T. 220 Kv max. 945 r, min. 700 r in nine days.

February 14 to March 23: Teleradium 10-gramme unit. Dose to primary max. 4,700 r, min. 2,850 r. Dose to skin 5,700 r in thirty-eight days.



FIG. 1.—18.1.50.



FIG. 3.—18.4.50.



FIG. 2.—25.1.50.

[Photograph taken after treatment has been kindly lent by Professor Smithers.]

There was considerable reduction in the size of the tumour and her general condition is good, as shown by the photograph (Fig. 3) taken on 18.4.50.

June 7, 1950: Examination now shows no evidence of residual tumour, but she has developed a secondary deposit in the innominate bone.

[*February* 10, 1950]

Demonstration of Honeycomb Lungs.—NEVILLE OSWALD, F.R.C.P.

The clinical, radiological and pathological features of a dozen cases are demonstrated in which there are thin-walled cysts distributed uniformly throughout the substance of both lungs. The frequency of spontaneous pneumothorax and of right heart failure is to be noted. The cysts may be part of a general disorder and occasionally occur in any of those three closely related conditions: the Letterer-Siwe disease, Hand-Schüller-Christian disease and eosinophilic granuloma of bone. They may be present in tuberous sclerosis and other similar mesodermal dysplasias, so far having been only recorded in adults. In the majority of instances, however, there is no evidence of disease outside the lungs, such cases falling into two groups. In children and young adults a developmental defect is the most likely cause and spontaneous pneumothoraces, frequently bilateral, are common. In later life infection plays a prominent part, with bronchitis and bronchiolitis leading to bronchiolar

distortion; spontaneous pneumothorax is unusual in such cases but death from right heart failure is likely to occur within a couple of years of the onset of troublesome symptoms.

The radiological features are characteristic but variable. In the developmental type thin-walled cysts are clearly seen; but associated bronchitis, heart failure or the infiltration of a general disorder may render them less distinct in a fully expanded lung. They are always much more easily detected during spontaneous pneumothorax. Iodized oil does not enter the cysts on bronchography.

Case report.—A sailor aged 27 was admitted to hospital with two months' history of cough and sputum. Five days before admission he woke in the morning with substernal pain and breathlessness. There was no significant previous history and radiographs taken as recently as eighteen months before had been passed as normal.

On examination his general condition was good and no physical abnormalities were detected apart from the signs of right spontaneous pneumothorax.

Radiographs and tomograms of his chest showed thin-walled cysts throughout both lungs, being more clearly seen on the side of the pneumothorax. (Figs. 1 and 2.)



FIG. 1.—Honeycomb appearance during spontaneous pneumothorax (tomogram).



FIG. 2.—Honeycomb appearance in expanded lung (tomogram).

His lung subsequently expanded and since then he has not been seen at hospital.

Comment.—The radiological appearances are those of the developmental type of honeycomb lung. It is possible that more spontaneous pneumothoraces may occur and that eventually he will develop right heart failure. The history of bronchitis for a few weeks before the lung collapsed is characteristic and it is possible that his infection threw an extra strain upon his thin subpleural bullæ.

REFERENCE

OSWALD, N., and PARKINSON, T. (1949) *Quart. J. Med.*, **18**, 1.

A Rib "Tumour".—G. E. VILVANDRÉ, M.R.C.S., L.R.C.P., F.F.R.

Patient, male, aged about 45, was sent to be radiographed with a suggested diagnosis of a lesion in the left upper zone. The history on further investigation was that four weeks previously he had had some elevation of temperature. He had not felt well for some time, and suffered from repeated colds. There was a pleural rub on the left upper region.

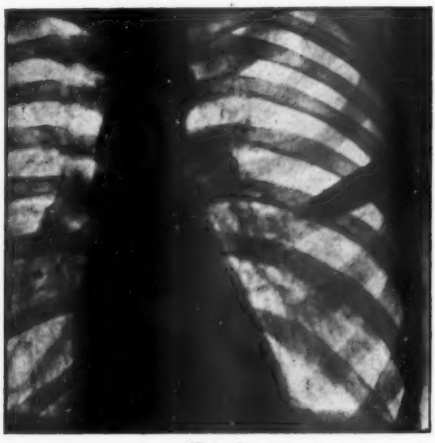


FIG. 1.

A chest radiograph showed a density of the fourth left rib, the lung fields were negative.

On examining the patient some swelling of the soft tissues was palpable. The possibility of a new growth was to be excluded. A Wassermann reaction was found to be negative, and a subsequent radiograph showed no appreciable change. Radiographs of the skull and pelvis showed normal bones and no suggestion of Paget's osteitis deformans.

There is, however, no evidence here of Albers-Schönberg disease and the irregular masses of condensed bone as seen in *melorheostosis* Léri are not present.

The diagnosis of Paget's disease in a single bone (rib), though not common, has been reported.

POSTSCRIPT (June 1950).—The case is being followed up and when last seen two or three months ago there was nothing new.

Wandering Pulmonary Infiltrations with Eosinophilia.—C. P. PETCH, M.D.

Mrs. M. P., aged 50.

History.—Admitted to St. Helier Hospital on four occasions, with wheezing respirations, cough and fever. The first two illnesses were severe, the third less so with only three weeks' fever, the fourth mild, with fever for only one week. In the intervals she has been perfectly fit apart from a feverish cold which was not accompanied by any chest signs or abnormality on investigation. She has never been abroad.

Examination during the acute phases showed rhonchi throughout both lungs, with areas of dullness and crepitations corresponding to the major radiological changes. A transient erythematous rash was attributed to a barbiturate sedative, and disappeared when the drug was withdrawn.

Investigations.—Radiographs of the chest show that opacities have appeared successively in all parts of the lung fields, finally with complete resolution. During what seems to have been her worst period, in 1946, small effusions obliterated the costophrenic angles, first on the right, later, when the right had cleared, on the left. Still later in this illness the cardiac shadow enlarged, but finally returned to normal. Each illness has been accompanied by a high white cell count and marked eosinophilia; figures for the 1946 attack are given:

	Total W.B.C.	% eosinophils	Total eosinophils
11.3.46	17,500	52	9,100
25.3.46	14,200	29	4,110
2.4.46	13,100	24	3,140
8.4.46	13,000	17	2,210
15.4.46	10,400	20	2,080
23.4.46	21,600	50	10,800
30.4.46	18,000	55	9,900
6.5.46	16,700	64	10,600
21.5.46	15,600	61	9,510
27.5.46	15,000	57	8,550
3.6.46	10,200	61	6,720
12.6.46	9,700	29	2,810

Similar counts were recorded in 1947 and 1949.

No evidence of metazoan parasitic infestation has been found. Sputum, urine, stools showed no significant abnormality. E.C.G. physiological.

Treatment has been on symptomatic lines. The administration of arsenic produced a violent reaction and was discontinued.

Comment.—This case differs from the rather similar group described by Löffler in being more severely affected. Tropical eosinophilia differs in its country of origin and response to arsenic. A case very similar to the present, with three relapses, has been recorded from the U.S.A. by Ham and Zimdahl (*Ann. intern. Med.*, 1948, **29**, 488). At present a descriptive title for the condition would appear best. Parasitic infestation (e.g. Ascaris) may produce a similar picture, but cannot account for all cases.

Dr. A. T. M. Roberts: These cases of transient pulmonary infiltration with blood and sputum eosinophilia usually arise in asthmatics, though in some cases the asthma or the eosinophilia may be absent. They do not form a precise clinical entity, but vary infinitely in symptomatology, severity and duration from a mild localized infiltration similar to Löffler's syndrome to a severe condition resembling, and often forming, part of the picture of polyarteritis nodosa. Pulmonary tuberculosis may be suspected and even carcinoma of the bronchus, if the lesion has a segmental distribution.

Pathologically, though atelectasis is suspected by some workers, it is more probable that the fundamental change is a hypersensitive reaction to a known or unknown antigen, occurring in the pulmonary blood vessels. In the mildest form a condition similar to skin urticaria arises, with capillary dilatation and exudation of serum into the surrounding alveoli. In more extensive cases, such as that shown, the reaction around the blood vessels is more severe and granulomata form, followed eventually by pulmonary fibrosis. This fibrosis may lead to scattered areas of characteristic "cyst-like" bronchiectasis. In the most severe cases areas of arterial necrosis occur indistinguishable from polyarteritis nodosa.

Pleural and pericardial effusions, containing eosinophils, are described in association with these infiltrations, and this patient's radiographs suggest that both these conditions may have been present.

Dr. Neville Oswald: I agree with Dr. Roberts that the infiltrations are probably in the nature of a vascular allergy and are comparable with other allergic manifestations such as urticaria and hay fever. Cases of this sort often have a formidable previous and family history. It is not unusual to start with hay fever in childhood, later to have suffered from asthma and then for the asthma to be replaced to some extent by transient infiltrations. After a period of months or years such patients may revert to their asthma.

Free Nipple Transplant in Breast Reduction and Breast Amputation (with Special Reference to Surgical Treatment in Obesity).—PATRICK CLARKSON, M.B., F.R.C.S.

One case, and photographs of others were shown illustrating free nipple transplants in breast reduction and breast amputation. This method is particularly suitable for the reduction of massive hypertrophy of the breasts, as it is a one-stage procedure in which a final result can be obtained by one relatively short operation. In contrast, the pedicle methods of breast reduction (such as the Biesenberger) have to be done in stages if the breasts are very bulky and dependent. Most cases in which the nipples are more than 3 in. to 4 in. below their normal level need a two-stage reduction if pedicle methods are used. The method of free nipple transplant is very suitable for extremely obese patients who want removal of most or all of the breasts.

The free transplant operation comprises an amputation of the nipples together with an area of about 1½ in. in diameter of the areola, and leaving the erector muscles under the nipple.

At a point 7 in. below the suprasternal notch and 4½ in. from the mid-line a circular area of epidermis 1½ in. in diameter is dissected off the dermis on each side. The amputated nipples are then fixed with many fine silk sutures over these dermal recipient sites. Four sutures transfix graft and dermis at the points of the compass close to the nipple. They are tied over a pad of dry gauze which compresses the nipple. Breast and skin, in excess of that needed to form a small mammary prominence under the nipple, is excised by elliptical incisions placed below the new nipple and including the old nipple site. In cases of extreme obesity



FIG. 1.—Breast amputation with free transplant of nipples. Shows pre-operative condition of breast. This patient's weight was stabilized at 16 st. (100 kilos).



FIG. 2.—Shows condition two weeks after operation for amputation of the breasts with free grafts of nipples which are complete takes.

a virtual amputation of the breast can be done. This method gives satisfactory results for such cases. In 7 patients all 14 nipples have been complete takes. The restoration of breast form obtained by it has not been as good as that obtainable by pedicle methods. There is some return of sensation to touch in these nipples over a period of a year but little other sensory response. The nipple grafts retain their erectile property.

Exfoliative Dermatitis with Low Plasma Protein, Œdema, Fatty Change in the Liver and a Filling Defect in the Stomach.—J. S. PEGUM, M.R.C.P. (for L. FORMAN, M.D.).

T. P., male, aged 67, a technical refrigerator engineer.

History.—In February 1948 developed a rash on arms and legs. By November the rash had become generalized and swelling of the ankles after exertion was noticed.

January 1949: Admitted to Joyce Green Hospital. The plasma proteins were low and in spite of bed-rest and a high protein diet became progressively lower and œdema increased.

May 1949: Transferred to Guy's Hospital. Generalized exfoliative dermatitis and genera-

lized œdema. Treated with choline and methionine by mouth and plasma transfusions with no improvement.

August 1949: Œdema relieved by mechanical drainage. Following this the skin improved and the œdema returned in lesser degree.

October 1949: Small hæmatemesis. Developed tense ascites.

Present condition.—Marked wasting. Skin shows large degree of recovery but there is marked pigmentation; tense ascites.

Investigations.—26.5.49: Liver biopsy—perilobular fatty infiltration.

22.7.49: Estimation of daily loss of protein through skin 19·3 grammes (average).

26.7.49: Plasma proteins total 4·9 grammes% (albumin 1·95, globulin 2·95).

24.11.49: Barium meal showed large filling defect of fundus of stomach.

This is a case of idiopathic exfoliative dermatitis with unusual features.

The generalized œdema developed after the dermatitis had been present for some months. Associated with this was a plasma protein level found to be consistently low during the period of observation. It was thought that loss of protein by skin exfoliation and exudation might account for the lowered plasma proteins. This loss was measured and found to be 19·3 grammes of protein per day.

A liver biopsy showed perilobular fatty infiltration.

The following explanations of this finding have been considered: (1) That the liver change was primary. (2) That the skin and liver changes were due to a common toxic factor. (3) That the liver changes were secondary to the skin condition due to the production by the skin of a toxic substance of the same sort as has been postulated to account for the liver changes in burns. (4) That the oils and ointments applied to the inflamed skin were absorbed, giving rise to a lipæmia with fat deposition in the liver.

A filling defect in the stomach revealed by barium meal together with complete achlorhydria are suggestive of carcinoma of the stomach.

The tense ascites was a relatively late development and may be due either to pressure from a metastasis on the portal vein or to the development of a cirrhosis of the liver.

POSTSCRIPT (June 1950).—The patient died on 1.4.50. At post-mortem the findings were as follows:

Anasarca, massive ascites and large bilateral pleural effusion. Considerable wasting masked by œdema.

Lungs: Œdema and bronchiolitis.

Cardiovascular system: Hypertrophy of left ventricle. Atheroma of coronaries and of aorta.

Liver: Small, but macroscopically normal. Histology showed areas of focal fibrosis.

Stomach normal: no evidence of carcinoma.

Congenital Bilateral Accessory Parotid Gland Hypertrophy. Cervical Sympathetic Overactivity Due to Scar.—G. QVIST, F.R.C.S.

Man, aged 58, with history of increased sweating on the right side of the face for three years, coming on after eating or smoking. In 1940 he noticed an enlarged gland in the right supraclavicular fossa which broke down and discharged for three months. This was treated with ultraviolet light. Slight discharge again in 1943 for short time.

Patient has had bilateral swellings on face as long as he can remember; diabetes diagnosed in 1948.

Family history.—Father had similar swellings on face. Father and brother have diabetes.

On examination.—(1) Bilateral enlargement of accessory parotid glands. The parotid space between jaw and ear feels empty. Confirmed by sialography. (2) Depressed scar in right posterior triangle fixed deeply. (3) On eating or smoking there is marked sweating on right side of face.

It is suggested that this is a case of stimulation of the cervical sympathetic, due to traction on the cervical scar by the muscles of deglutition (Fig. 1).

This is quite separate from the condition of enlarged accessory parotids which seems to be congenital in origin and is probably unassociated with the sweating syndrome (Fig. 2).

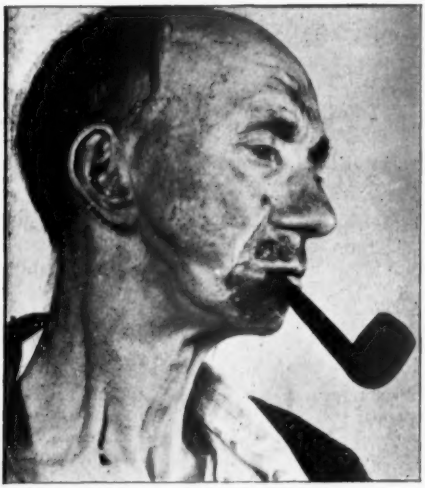


FIG. 1.—Showing scar in neck and sweating of right side of face demonstrated by dye.

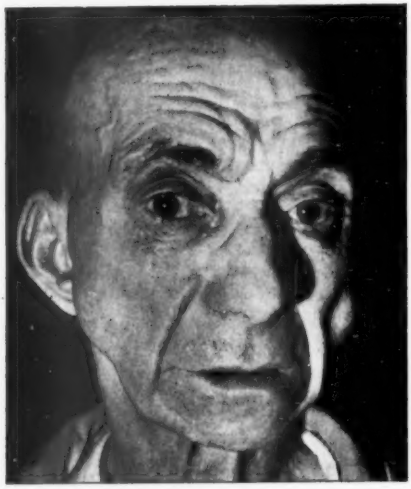


FIG. 2.—Showing bilateral enlarged accessory parotids.

Dr. F. Parkes Weber said he regarded Mr. Qvist's case as an analogue or variant of the auriculo-temporal syndrome (*see* F. P. Weber, *Trans. Clin. Soc. Lond.*, 1898, **31**, 277, and "Rare Diseases and Some Debatable Subjects", 1946, p. 66). In typical cases the scarring is in the parotid region, whereas in Mr. Qvist's case it is just above the sternal end of the clavicle and the sweating associated with eating extends over a large area. The abnormality in the position of the parotid glands is doubtless congenital and has nothing to do with the abnormal sweating.

Section of Otology

President—GAVIN YOUNG, M.C., M.B., F.R.F.P.S.Glas.

[*February* 3, 1950]

The Surgery of Otosclerosis

By TERENCE CAWTHORNE, F.R.C.S.

IN December 1946 I gave a Review of the Surgery of Otosclerosis (*Proc. R. Soc. Med.*, **40**, 320) and I should now like to submit some personal impressions and experiences of this fascinating and expanding branch of Aural Surgery.

What I have to say will be based on personal experience in over 400 operations for otosclerosis and some 250 operations on the labyrinth for other non-suppurative conditions.

The operation in general use and which I employ is based on Lempert's nov-ovalis approach, and consists in making a window in the anterior part of the bony external semicircular canal and adjacent ampulla. This opening is covered by a flap derived from the skin covering the anterior wall, roof and posterior wall of the bony external meatus, continuity with the intact tympanic membrane being preserved.

Its proper performance makes considerable demands on the surgeon and calls for practice, patience and self-control. The surgeon must ensure that he is provided with good illumination and adequate magnification, particularly for the most important part of the operation, namely the making of the fenestra. This must be made on top of a mound, so that when the tympano-meatal flap is placed over the fenestra it will invest it closely and seal it off like a rubber patch sealing off a puncture in a pneumatic tyre. Great care must be taken to avoid injury to the membranous labyrinth, or anything that may encourage the formation of excessive fibrous tissue or bone formation over or within the fenestra. Hæmostasis, a fenestra with clean margins, a perilymph space free of blood and of bone debris, an intact membranous canal and ampulla, and a thin intact tympano-meatal flap from which all flakes of bone have been removed, are essential for success. Lempert and his former pupil, Shambaugh, have furthered the progress of the operation by drawing attention to these and other factors. From my own experience I would like to emphasize the value of adequate magnification whilst making the fenestra. A binocular dissecting microscope, which is freely manœuvrable and which has a brightly illuminated field is, I believe, the surest way of achieving a clean fenestra, a clean flap, an undamaged membranous labyrinth and a perilymph space free from bone debris and blood.

Only when this stage of the operation is properly performed can a good and lasting improvement in hearing be expected. The following photographs (Figs. 1, 2 and 3) show the fenestra as it appears at operation under a continuous flow of saline. They are enlargements from the 16 mm. colour cinefilm taken by Mr. E. Gwynne Evans and Mr. Edward Mackie which will be shown at the end of the paper.

Therefore, the closest attention and much practice have to be devoted to the making of the fenestra, and the wise surgeon will ensure that he is not tired out by the preceding steps of the operation, cramped for space by inadequate exposure, handicapped by poor illumination, nor, finally, embarrassed by lack of experience in working in a magnified field.

Other aspects of the operation have been fully dealt with elsewhere, and, provided that the exposure is adequate, both at the time of operation and for the post-operative inspection and treatment of the cavity, and that important neighbouring structures are not imperilled, the details of the soft tissue and bony approach can be left to the individual surgeon. My own preference is for the endaural approach, though, as I have seen when visiting Mr. Simson Hall in Edinburgh, the post-aural approach gives an excellent view. I have still, however, to be convinced of the value of the antauricular approach advocated by Popper.

The bony cortex of the mastoid can be reduced to bone dust by a dental drill or removed by sharp gouges. The drill has the advantage of being more bloodless and, in practised hands, can be very accurate and safe. On the other hand, the reduction of the mastoid cortex to fine bone dust by a drill is a messy, laborious and time-consuming procedure. Having tried

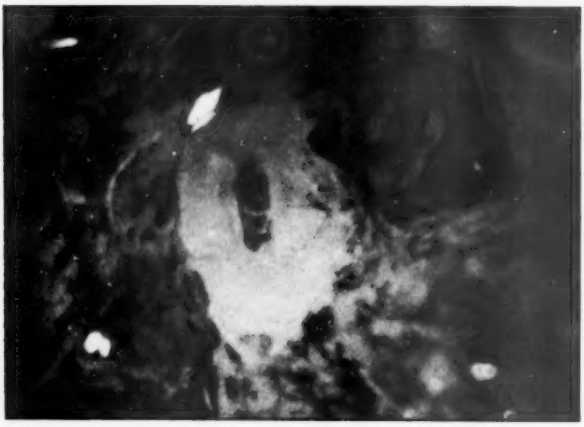


FIG. 1.—Magnified view (× 6) of a newly created fenestra. The top of the fenestra has been cut off and turned over, where it can be seen to the left of the fenestra. The membranous canal with some shreds of endosteal debris and bone will have to be cleared away.

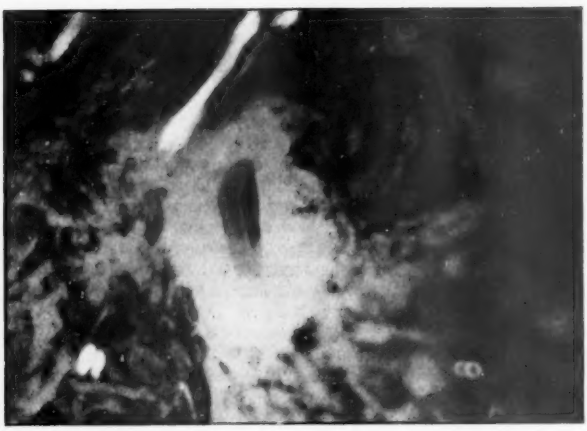


FIG. 2.—The same fenestra as in Fig. 1, after all the shreds of bone have been cleared away.



FIG. 3.—The completed fenestra. The membranous labyrinth can be clearly seen and in the upper part of the fenestra the membranous canal can be seen bending into the ampulla (× 10).

both, I prefer a little blood at this stage to a lot of bone dust, though of course both can be, and are, satisfactorily removed by flushing the cavity with warm saline. In this connexion I should like to emphasize the value of irrigation of the operative field with saline at 100° F. In the earlier stages intermittent irrigation is sufficient, but for making the fenestra continuous irrigation as suggested by Shambaugh is most helpful. It is, however, of some importance to ensure that the irrigating fluid is constantly at 100° F.; for the exposure of the unprotected vestibular labyrinth to gross thermal changes is obviously undesirable, and may augment the post-operative vestibular disturbance.

After removing the head of the malleus, I always cut the tendon of the tensor tympani where it is inserted into the neck of the malleus. By doing this I believe the chance of troublesome clicking or vertigo on contraction of the tensor tympani after the operation is reduced.

Sufficient bone must be removed to allow full freedom of movement under magnification in the region of the fenestra. Aubry, van Eyck, Dohlman, Popper and, lately, Shambaugh advocate a very limited removal of bone and they try to avoid opening the mastoid or even the antrum. I have not, as yet, any experience of this limited approach, though if it will hasten post-operative healing without increasing the risk of undesirable complications from infection it will be an advantage. Skin grafting the raw areas of the bony cavity at the time of operation helps to shorten the healing time.

For the first few post-operative days, the tympano-meatal flap and cavity need to be subjected to continuous, gentle and non-adherent pressure. This can be achieved by lining the cavity with strips of oiled silk—Lister's Green Protective—and then packing it with small pieces of marine sponge. Shambaugh, from whom I got the idea of using sponge, employs two relatively large pieces soaked in sulphadiazine cream, but I believe that smaller pieces give a more evenly distributed pressure, and I am not as yet convinced that any local antiseptic is of value.

With regard to the post-operative period, some vestibular disturbance is the rule, due not so much to infection, as has been suggested by some observers, but to the altered physical conditions within the labyrinth. This can best be overcome by the head and balancing exercises developed by Cooksey and myself for the management of the disturbance of balance following vestibular injuries. Campbell has recently reported on the value of dramamine in combating the post-operative vestibular disturbance. Most patients are out of bed on the fourth post-operative day, and leave hospital within the fortnight.

Some degree of post-operative infection of the cavity is common, and though continued discharge may be a nuisance it rarely affects the hearing result, and seems to be due to infection of soft tissue rather than bone.

The results are largely governed by the care with which cases are selected and the skill with which the operation is carried out.

Before, however, considering the selection of cases, I should like to deal with operative results.

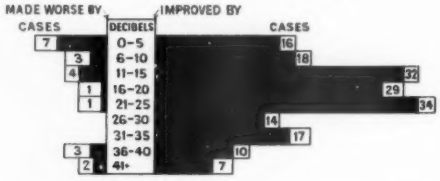
Results.—Now when we come to the recording of results, I must confess that I am somewhat at a loss to know how best this should be done. In fact, I would go farther than this and say that no one person, least of all the reporter himself, is in a position as yet in which he can say what is the fairest—or should I say wisest—way of doing this. It is mainly by watching his results that the surgeon can measure his progress and be stimulated to seek for further improvement. Furthermore, by reference to his own results he can offer the most likely and, therefore, the fairest estimate of the amount of improvement in hearing that fenestration in his hands will offer.

Many standards have been suggested for reporting results and the American Otological Society has a sub-committee to enquire into standards for reporting fenestration results, which has already made provisional suggestions. It would, I think, be a great help to all who are interested in this work, if a committee could be set up in this country as well to advise on the best way of recording the results of the fenestration operation, and I would venture to suggest that this Section would be a very appropriate body to undertake such a task.

With regard to my own results, I would prefer to give the figures in terms of decibel improvement or loss for pure tones within the critical range of speech frequencies (512, 1,024 and 2,048 c.p.s.). I have grouped the cases in 5-decibel steps and have included only those patients who have been followed up for eighteen months or more after operation, and I have chosen this time because so far I have not had any patient whose hearing deteriorated after eighteen months. I think that the ideal way of testing the hearing capacity after operation is by means of recorded speech, and Silverman and Walsh have already published some interesting observations along these lines.

The results now to be considered are those from cases on whom I operated by the technique described, between July 1946 and August 1948. Only those of whom I have no record for at least eighteen months after the operation have been omitted.

TABLE I.—HEARING FOR PURE TONES WITHIN THE CRITICAL RANGE OF SPEECH FREQUENCIES (512, 1,024 AND 2,048 C.P.S.) EIGHTEEN MONTHS OR MORE AFTER FENESTRATION FOR OTOSCLEROSIS IN 198 CASES (INCLUDING 5 REVISIONS).



The selection of suitable condidates for surgery from among those deafened patients who hopefully present themselves is no easy task, nor is it a matter about which hard-and-fast rules can be laid down.

The series under consideration does not include any patient who:

(1) Was not thought to be suffering from otosclerosis.

(2) Did not have an intact and healthy tympanic membrane.

(3) Could not tolerate and understand speech with the help of a high quality amplifier.

Each patient selected for operation has, at the time of the first interview, been put into one of three groups, Suitable, Borderline, and Unsuitable, and the distribution in this series has been as follows:

TABLE II

Suitable	..	..	..	107
Borderline	..	..	..	80
Unsuitable	..	..	..	11

In classifying a case of otosclerosis in terms of suitability for operation it is necessary to assess the patient as a whole; taking into consideration the history, the appearance of the tympanic membranes, the tone of the voice, tuning fork and pure tone audiometer tests, and the ability to understand amplified speech. In the present state of our knowledge, I hesitate to give precedence to any one of the significant features of the clinical picture of otosclerosis that I have just mentioned in selecting cases for operation. Instead I would prefer to give, in summarized form, a typical case from each of the three groups.

TABLE III.—SUITABLE

Mrs. O. D., aged 48. History of progressive deafness ten years. Not affected by birth of only child. Hears better in noisy surroundings. No history of deafness in family.

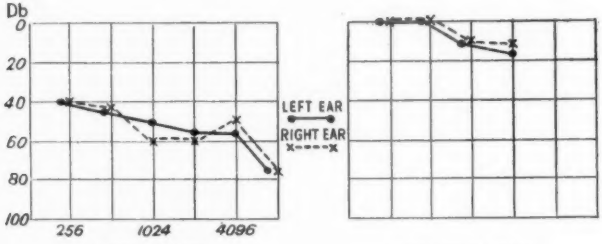
On examination.—Upper respiratory tract healthy. Soft voice of normal timbre.

Tympanic membranes: Intact, normal lustre, mobile on auto-inflation.

Speech (at conversational level): Unamplified, 3 inches; amplified, 12 feet.

Tuning forks (512, 1,024 and 2,048 d.v.): All negative Rinne and normal bone conduction.

Pure tone audiometer: Maico D.9.



Air conduction. Bone conduction.

Conclusions: Otosclerosis with unimpaired cochlear function. Suitable for fenestration. 50% chance hearing speech at 10 feet. (Operation resulted in hearing speech at 20 feet.)

TABLE IV.—BORDERLINE

Mrs. E. D., aged 45. History of slowly progressive deafness 31 years. Not affected by birth of only child. Hears better in noisy surroundings. History of deafness on mother's side of family.

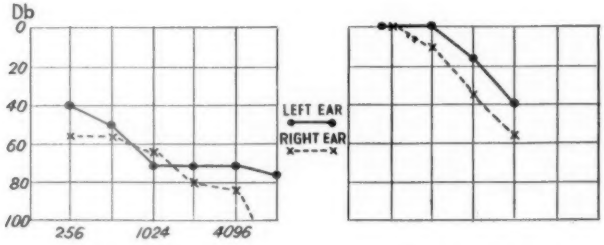
On examination.—Upper respiratory tract healthy. Soft voice of normal timbre.

Tympanic membranes: Intact, normal lustre, mobile on auto-inflation.

Speech (at conversational level): Unamplified, not heard; amplified, 6 feet.

Tuning forks (512, 1,024 and 2,048 d.v.): Negative Rinne 512 and 1,024. Not heard left, and heard by bone only right, 2,048. Reduced bone conduction 1,024 and 2,048.

Pure tone audiometer: Maico D.9.



Air conduction. Bone conduction.

Conclusions: Otosclerosis with slight impairment of cochlear function. Borderline for fenestration. 30% chance hearing speech at 3 feet. (Operation resulted in hearing speech at 8 feet.)

TABLE V.—UNSUITABLE

Mr. F. C. H., aged 43. Progressive deafness sixteen years. Hears better in noisy surroundings. Brother also deaf.

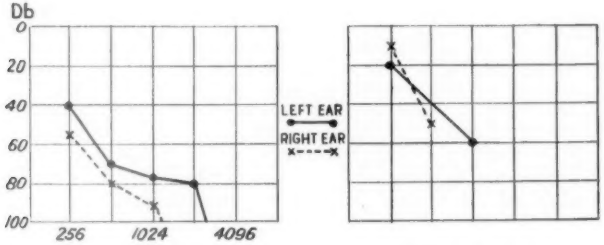
On examination.—Upper respiratory tract healthy. Slight alteration in timbre of voice.

Tympanic membranes: Intact, normal lustre, mobile on auto-inflation.

Speech (at conversational level): Unamplified, not heard; amplified, 4 feet.

Tuning forks (512, 1,024 and 2,048 d.v.): Negative Rinne 512 and 1,024 right. Air equals bone 512 and 1,024 left. Positive Rinne 2,048 left, not heard right. Reduced bone conduction 512, 1,024 left and right, and 2,048 left.

Pure tone audiometer: Maico D.9.



Air conduction. Bone conduction.

Conclusions: Otosclerosis with considerable impairment of cochlear function. Unsuitable for fenestration. 20% chance hearing conversation at 1 foot. (Operation resulted in hearing remaining unchanged.)

The following tables show the results in each of the three groups:

TABLE VI.—HEARING FOR PURE TONES WITHIN THE CRITICAL RANGE OF SPEECH FREQUENCIES (512, 1,024 AND 2,048 C.P.S.) EIGHTEEN MONTHS OR MORE AFTER FENESTRATION FOR OTOSCLEROSIS IN 107 CASES CLASSIFIED AS SUITABLE.

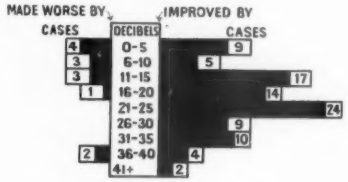


TABLE VII.—HEARING FOR PURE TONES WITHIN THE CRITICAL RANGE OF SPEECH FREQUENCIES (512, 1,024 AND 2,048 C.P.S.) EIGHTEEN MONTHS OR MORE AFTER FENESTRATION FOR OTOSCLEROSIS IN 80 CASES CLASSIFIED AS BORDERLINE.

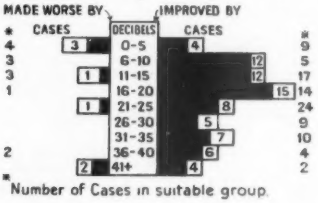
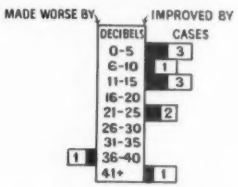


TABLE VIII.—HEARING FOR PURE TONES WITHIN THE CRITICAL RANGE OF SPEECH FREQUENCIES (512, 1,024 AND 2,048 C.P.S.) EIGHTEEN MONTHS OR MORE AFTER FENESTRATION FOR OTOSCLEROSIS IN 11 CASES CLASSIFIED AS UNSUITABLE.



It will be seen from the foregoing tables that the classification of cases is an uncertain business. Some classified as unsuitable do well, whilst others thought to be suitable do badly. In estimating to the patient at the time of the first consultation the chances of success, I have in the past offered suitable cases a 50% chance, borderline a 30% chance, and some unsuitable cases a 20% chance of long-term improvement in hearing. The extent to which the hearing is likely to be improved by operation is of course governed by the original hearing loss. I estimate this on the basis of a possible improvement of 25 decibels for the critical speech frequencies and translate this into terms of everyday hearing.

Indications.—Now I believe that in its present form the fenestration operation is most likely to be successful when the otosclerotic bone is limited to the region of the oval window, and *per contra*, that extensive spread of otosclerotic bone, either over the surface or into the cavities of the bony labyrinth, renders a case unsuitable. Therefore any clinical indication of such extensive growth should be carefully sought for, and, if present, taken into consideration in assessing suitability for operation.

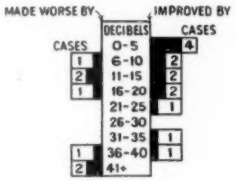
In my previous review of the surgery of otosclerosis I mentioned four signs of poor prognostic significance, and I should now like to add a fifth.

TABLE IX.—SIGNS OF POOR PROGNOSTIC SIGNIFICANCE

(1) Alteration in the *timbre* of the voice.
(2) Intolerance of *amplification*.
(3) Disappearance of *paracusis*.
(4) Reduction of *bone conduction*.
(5) Pink-tinged *tympanic membrane*.

I would suggest that in the first three groups the organ of hearing is definitely at fault. In Group 4, the organ of hearing may be responsible, but I believe that loss of bone conduction can also be caused by widespread otosclerotic bone, particularly if it seals up both labyrinthine windows. In the last group, the tympanic membrane is seen to have a pink tinge due, it is believed, to transmitted colour from the mucosa covering the promontory —the so-called Schwartze sign. This is often associated with other unfavourable signs, particularly loss of bone conduction, and is generally regarded as an unfavourable sign.

TABLE X.—HEARING FOR PURE TONES WITHIN THE CRITICAL RANGE OF SPEECH FREQUENCIES (512, 1,024 AND 2,048 C.P.S.) EIGHTEEN MONTHS OR MORE AFTER FENESTRATION FOR OTOSCLEROSIS IN 20 CASES WITH PINK-TINGED TYMPANIC MEMBRANES.



In the present series, 20 cases were noted as having pink-tinged tympanic membranes, and only 7 of these sustained an improvement of more than 10 decibels for the critical speech frequencies, despite the fact that 12 had been assessed before operation as suitable cases. On the other hand, 7 were made worse. Until I was reviewing the present series of cases I did not fully appreciate the grave prognostic significance of pink-tinged tympanic membranes. I have found that such cases have been the cause of much disappointment, and in future I shall put all such cases in the "borderline" or "unsuitable" category; though by doing so I do want to emphasize that they should not be denied operation provided that they appreciate that the chance of success is slender.

The cause of failure in some instances is only too obviously—and I refer to my own cases—faulty technique, in others faulty selection, and there are some in which the cause of failure is not obvious; but it is only by doing a certain proportion of apparently unsuitable cases that we can advance this work. In 3 out of the 11 apparently unsuitable cases that I operated upon, there was an improvement in hearing of more than 20 decibels for the critical speech frequencies. Therefore although the prospect of improvement is not necessarily bright in cases classified as unsuitable, I do not think that they should be denied operation if there is evidence of effective cochlear function.

Before concluding, I should like to offer a few observations on two other forms of surgical treatment that I have tried.

Removal of stapes.—I have removed the stapes in 23 cases of otosclerosis, all but 4 of which would be classified as "unsuitable". One of the "suitable" cases has retained his improvement for nearly four years. If we can solve the problem of sealing off the oval window and of retaining the tympanic membrane intact and of normal tension, I believe that this might prove to be a most effective and lasting form of treatment, because, after all, it is the natural window; and once the stapes has gone, is unlikely to become sealed over by bone again, as anyone will realize who has seen the oval window under the dissecting microscope.

In another small group, all considered unsuitable, I have performed a fenestration operation and in addition removed the stapes. In all the 4 cases so treated, I believed that the round as well as the oval window was impeded by otosclerotic bone. In none, however, was there any improvement in hearing; but I still hope that in such cases, provided that there is sufficient cochlear function to appreciate and tolerate amplification, some form of operative treatment may be found to be of help, and I intend to continue to search for it.

Sequelæ.—There are two final aspects of this problem that are of considerable physiological interest and which may help us further to appreciate the mechanics of hearing.

I have not, as yet, seen a case of otosclerosis submitted to the fenestration operation in which exposure to loud sounds resulted in a vestibular stimulus. Readers will recall the Tullio phenomenon in which a window made in the lateral canal renders the animal—pigeons, in the cases Tullio described—liable to a vestibular stimulus on exposure to a loud sound.

I had a patient, suffering from Ménière's disease, on whom in 1938 I made an opening into the bony lateral semicircular canal, without disturbing the membranous labyrinth. This patient, after leaving hospital, complained that exposure to any loud sound caused giddiness, and investigation revealed that exposure to a pure tone of 80 d.b. within the range 250–4,000 c.p.s. caused a movement of the eyes and deviation of the head and body. This was relieved by a second operation, in which the membranous external semicircular canal was removed and, as a result, cochlear function destroyed.

Now why is it that Tullio's phenomenon is not seen after the fenestration operation for otosclerosis? For I have not as yet seen it, nor have I knowledge of any record of it. I think that the reason may well be that the Tullio phenomenon is dependent upon unimpeded round and oval windows. I have seen 3 patients suffering from severe and intractable vertigo following a fenestration operation. In each case there was reason to suspect that the foot-plate of the stapes was not impeded by otosclerotic bone. In each case also the hearing had been made worse by the operation and it seemed advisable to consider destroying the remaining but clearly disordered vestibular function. Up to the present I have not seen such a sequel in otosclerosis, though as Shambaugh points out it can occur. I do feel that an artificial opening in the bony vestibular labyrinth is particularly liable to cause troublesome vertigo if the natural openings are unimpeded. For this reason I would hesitate to advise the fenestration operation where there was any reason to suppose that the stapes was mobile.

The other feature that is of particular interest to me is that limited damage to the membranous canal does not, in cases of otosclerosis, necessarily result in a complete loss of hearing. In every case of Ménière's disease in which I have removed all or even part of the membranous semicircular canal, total and irreversible deafness has resulted. I have, however, accidentally torn the membranous external semicircular canal across in 4 of the cases in the present series. In none was the hearing improved; whilst in 3 it was not altered by more than 10 d.b. either way, in the fourth it was made much worse, but was not abolished. In each case the membranous canal was torn across at the posterior end, well away from the ampulla. I hope in due course to report the result of deliberately carrying out a similar procedure in cases of Ménière's disease.

I have some patients whose ear continues to discharge, though this does not necessarily modify a good result; whilst others have a varying degree of narrowing of the meatus.

As yet I have not found it necessary to re-operate on a patient for either of these complications.

In 2 cases there was a facial paresis that cleared up within two weeks. In 31 cases the initial improvement was not maintained, due, I believe, in most instances to a partial or complete closure of the fenestra. On the other hand, 20 cases continued to improve three or more months after the operation, and one only started to improve seventeen months after operation. Finally in one case the hearing in the operated ear was lost entirely. Because of the possibility of making the hearing in the operated ear worse, I make it a rule to operate always on the worse hearing ear first. If this is successful, the other ear can, if desired, be operated on at a later date—not less than a year after the first operation.

With regard to revision operations, I must confess to being disappointed in the results. In the five that I have done in the series under review, I found bone extending into and, as a rule, surrounding the membranous canal. In three of these, the membranous canal was torn in endeavouring to free it from the surrounding bone. In none was there any permanent improvement in hearing as a result of the revision operation. I think that the next time I undertake a revision I shall be prepared if I find the membranous labyrinth entangled in new bone to make a fresh opening in the bony labyrinth, possibly in the posterior canal.

I should like to take this opportunity of saying how much I appreciate the generous help of my friends here and elsewhere for their kindness in entrusting their patients to my care. There is still much more work to be done and many problems to be solved. Above all we should not regard otosclerosis as a purely surgical problem and we should not lose sight of the fact, nor should we let our patients lose sight of the fact, that a good wearable valve-amplified hearing aid rarely fails to improve the hearing in cases of otosclerosis, and that surgery is only part of the management of the patient suffering from this form of deafness.

Finally, I should like to recall the names of those who have made this work possible, and in particular I would mention Jenkins, Holmgren, Sourdille, Lempert and Shambaugh, and to say of them as did Shakespeare in "The Tempest": "Your tale, Sir, would cure deafness."

Mr. E. R. Garnett Passe: *Technique.*—Three major controversies have arisen in the technique of the fenestration operation, namely:

(1) Should we exenterate the mastoid process, or should we be content with as small an approach in the form of an atticotomy as possible, either by the end- or the pre-aural approach? Having used both extensively I am whole-heartedly in favour of the mastoid being exenterated for the following reasons. It is possible to make my long fenestra with a protecting "hood", and to construct and position the flap more carefully, and to facilitate the subsequent dressings with less risk of post-operative infection or excessive granulation tissue formation.

(2) The second question is in the use of the lead burr. Personally I am awaiting the published reports on cases of two years' duration from those using this technique. In the few cases I have used it, sufficient time has not yet elapsed to judge of its value. I feel that the presence of any *noxious foreign body* must *increase* the tendency to excessive fibrous tissue formation from the under-surface of the flap, which, when it occurs, undoubtedly decreases the hearing.

(3) Thirdly, it has been suggested recently by Holmgren that it is not necessary to open the endosteum. Even under a magnification of 10, I find it almost impossible to clean the endosteum of all bone dust and chips without opening into the perilymphatic space. If I can preserve the endosteum I like to turn it down over the lower edge of the fenestration as suggested by Sullivan.

As one of the causes of failure in the restoration of hearing is obstruction of the round window with blood clot, I make a routine practice of thoroughly examining the foramen before proceeding to construct the fenestra. In order to keep the foramen clean during the construction of the fenestra I place in it a small piece of lintene attached to a thread. At the completion of the fenestra the pack is removed.

Healing of the cavity.—It soon became evident to me that the rate of healing was in direct ratio to the dryness of the cavity. Of great help in this respect are frequent dressings and the use of calgitex [1] which I introduced with Blaine in 1948. Skin grafting of the cavity enjoys a certain popularity, but I think that the risk of introducing infection in this way is unjustified. I find my large meatal graft and careful post-operative dressings quite adequate.

The employment of the recruitment test in borderline cases is a great help. I cannot agree with Mr. Cawthorne's observation *re* the inadvisability of operating on cases which show a pinkish tinge of the drum head—surely this may only mean that the membrana tympani is, perhaps, unusually thin.

Results.—Sufficient time has now passed since the fenestration operation was first performed in this country for us to begin to form our own opinion of its value without having to rely entirely upon the results obtained by otologists of other countries. However, there is still a dearth of published records by those of us who are making a specialty of the operation. On reviewing my results which I published last year [2], I find that there has been only slight material change in the percentage of overall improvement. Of my second series performed between three and four years ago the percentage of cases remaining at the practical level is still about 40%. These were all cases of cartilage stopple insertions. During the next three years 611 cases were operated on and from those cases whose audiometric records are available, comprising all groups, the following results were obtained:

Three-year-old cases—Just over 70% showed a maintained hearing improvement of over 11 decibels.

Two-year-old cases—73% showed a maintained hearing improvement of over 11 decibels.

A maintained hearing improvement of 11 decibels or more does not necessarily mean that the patient's hearing was maintained at the 30 decibel level. To my mind there can be no more difficult assessment of an operation result, for what improvement satisfies one patient does not necessarily satisfy another.

The fact that over 40 successful cases have had the operation performed on the other ear at their own request speaks volumes for its value.

REFERENCES

1 PASSE, E. R. G., and BLAINE, G. (1948) *Lancet* (ii), 651.
2 —— (1949) *J. Laryng. Otol.*, **63**, 495.

Mr. J. P. Monkhouse spoke of the difficulty of predicting results and said that he had obtained very marked improvement in some of the most advanced cases. These were often older people and the improvement seemed to last better than in some which might have been thought to be more favourable.

The assessment of results or of the value of a change of technique was necessarily a lengthy process and otologists should pool their knowledge and experience, but before they could do this, they must speak a common language. He felt that this meant the use of speech audiometry, since pure tone audiometry could err, sometimes suggesting a better and sometimes a worse hearing for words than was actually the case. However, as they had just heard, there were pitfalls in speech audiometry and a standard and reliable technique would have to be evolved.

The results at the Middlesex Hospital had been assessed on pure tone audiometry and the patient's own opinion had been entirely ignored.

Cases had been graded into "Very good"—over 35 decibels improvement; "Good"—25–35 decibels; "Moderate"—15–25 decibels; "Slight improvement"—5–15 decibels. Anything up to 5 decibels was considered as showing no change. The marking had been strict.

In the earliest series of 19 cases, in which a stopple was used, there had been an immediate improvement of some degree in 74% but now, after three years, only 16% retained any gain.

A series of 28 cases, without stopple but with a long fenestra and all two or more years since operation, showed an immediate improvement of 87%, falling after two years to 52%. The detailed figures were of interest: "Very good" 43% falling to 6%; "Good" 32% falling to 18%; "Moderate" 11% falling to 3%; "Slight improvement" 3% rising to 25%; "No change" 0% rising to 18%; and "Worse" 11% rising to 30%.

The following 14 cases operated upon more than eighteen months but less than two years ago showed approximately the same percentage (85%) of immediate improvement and to date 72% were still improved. Failure after a primary success seemed to occur around six months or at about eighteen months after operation, and since these cases had all passed the eighteen-month mark, he had hopes that they might show a better result than had the earlier series.

Mr. C. A. Hutchinson asked Mr. Cawthorne whether he had noticed any improvement in the hearing of the other ear after fenestration. The speaker noticed that using exactly the same audiometer at intervals of six months, a year and two years post-operatively, in a good case there appeared to be some improvement in the other ear.

He agreed as to a pink tympanic membrane being an index to a poor chance. Cases showing the "flamingo-pink" tinge did not do well with fenestration. He was interested to note that both Mr. Cawthorne and Mr. Garnett Passe referred to the need for an unobstructed foramen rotundum for a good result. When there was a poor result after what appeared to be a perfect technical procedure there might be some further improvement if a second fenestration was done through the promontory and covered with a flap of mucous membrane. He was experimenting along that line at present.

He did not use the same approach as Mr. Cawthorne. He agreed with Mr. Simson Hall and used the postero-superior approach, but whichever approach was used the technique inside was almost identical. Whether it was done pre-meatally or post-meatally one was faced with the bugbear of bleeding. One could cope with it up to a point by preliminary injection of the field with adrenaline saline. It was a great help, he found, to make use of continuous-flow saline adrenaline and small "postage stamps" of gelatin sponge; there were three sizes 1, 2 and 3; 3 was the most useful. One or more could be applied dry over an oozing area, left in place for twenty seconds when all the bleeding stops.

He would like to congratulate Mr. Cawthorne on his paper and admirable film.

Mr. A. Brownlie Smith said that he would have liked Mr. Cawthorne to have given some figures of the result of the operation according to the different age-groups. Otosclerosis was usually a more acute disease in the young and from his own cases he had found that the best and most permanent results were those obtained in older people where the disease had slowed down or stopped and where the bone regeneration was not so efficient as in younger people. He had found it difficult to decide whether to operate on young otosclerotics or not. He had a young girl of 16 under his care at present and he felt she might obtain a marked improvement in the hearing from the operation but, afterwards, be just as bad, if not worse, than before.

Dr. G. I. Henderson (*Dundee*) said that he had found that bleeding during operation had been considerably reduced by the type of anæsthesia used. The desired conditions had been obtained mainly by the intravenous injection of omnopon at the time the intratracheal tube was passed while light trilene was administered.

Mr. W. G. Scott-Brown advocated the use of a plastic or tantalum stopple and it was for that reason that he had sent all his cases to Air Commodore E. D. D. Dickson for the last six months for testing before and after operation. He had a small series of cases to record: in 1946 he operated on 20 cases and of these 4 had over 25 decibel improvement; 8 had over 15 decibels, and 5 had under 15 decibels; 3 remained the same or were worse. In 1947 there was a series of 21 cases; 7 obtained over 25 decibel improvement, 6 over 15 decibel improvement, and 5 under 15 decibel improvement—which did not give any very useful improvement. 3 were the same or made worse. The advantage of the stopple was that the operation was simplified and a fewer number of cases required reopening. He had only had to reopen 3 of the cases reported.

There was one interesting feature since he had used stopples with a larger hole through them. In cases with good hearing result there was practically no giddiness on touching the stopple. He asked Mr. Cawthorne for an explanation and he suggested that the displaced perilymph could "escape" up the canal through the stopple and so minimize the flow of perilymph along the canal.

Mr. R. Scott Stevenson said that no one had a greater admiration than himself for Mr. Cawthorne and his work, but he felt he had to ask one or two questions with regard to his paper. The first was about the criterion for operation. Looking at the audiograms that had been shown, he would say that the last 2 patients were cases of nerve deafness and to such patients he would say, "Go and get a hearing-aid and learn lip-reading". Hearing-aids and lip-reading were very helpful to such people, and it was wrong to persuade them to have a fenestration operation when the case was admitted to be so unfavourable. Otologists looked to Mr. Cawthorne for guidance on when to operate and in this paper they did not get it. He recognized Mr. Cawthorne's honesty of purpose, but if he operated on such patients, what were other people going to do? Mr. Cawthorne had started off by saying that the disease of otosclerosis was no longer obscure, but that was not really true. It was probably even more obscure to-day than it seemed to be before, and one did not know any more about the cause of otosclerosis to-day than was known one hundred years ago. Otologists must not be lured away by beautiful technique; it was always something to be suspicious of rather than to admire.

Mr. R. G. Macbeth said that Mr. Cawthorne had referred to his lack of experience of the Popper approach to this operation. In a series of about 100 cases the speaker had done 15 by the Popper approach. It looked very good in the pictures, it was very good in the post-mortem room, but when it was tried on the living it was a needlessly difficult operation to perform. Not only did the surgeon find himself mixed up with a plexus of veins in relation with the parotid fascia, but the access to the dome of the vestibule was restricted and he might have to become ambidextrous with the dental drill. The chance of post-operative scarring and stenosis was very much more marked than by the more traditional routes, and the chance of sepsis from the meatus seemed greater. It might be thought a little unfair to condemn the approach on a basis of 15 cases, but when the speaker reverted to the Lempert type of approach, he had been struck immediately by the fact that this was a much easier operation. The chorda tympani nerve was seen more readily by the Popper approach, but this seemed its only advantage.

Mr. F. McGuckin thought there might be some scientific interest in the audiometric recording of minor post-operative changes; but it would be well to realize frankly that improvements of the order of 5 or 10 decibels, perhaps even of 15 decibels, represented clinical failure from the viewpoint of the patient.

Mr. T. Cawthorne, in reply to the discussion, said he was interested in Mr. Garnett Passe's remarks and particularly in what he said about the round window. He had used the lead burr in a number of cases, but seeing, under the microscope, fragments of lead dropping into the perilymphatic space made him uneasy, so he had given it up.

Mr. Monkhouse and Mr. Brownlie Smith both brought out the point with which he entirely agreed, namely, that older cases did better. He was sure cases did better from the late thirties and forties onwards. He had had 4 cases which had been submitted to operation over the age of 60 and they had all done well. Unfortunately one must operate on some of the young people who have a rapidly progressing form of deafness but the results were sometimes disappointing. He had not analysed the results for different age-groups in this series.

Mr. Hutchinson asked about the question of improvement of hearing in the unoperated ear. He was particularly interested to hear that this was noticed in those patients whose hearing was much improved by operation. He thought it probable that when the ear not being tested was adequately masked, any apparent improvement would disappear.

With regard to what Mr. Scott Stevenson had said he hoped that he had not given the impression that he operated on every case he saw. He had agreed to operation in about 600 cases out of 1,100 cases of otosclerosis which he had seen during the past four years. Most of those classed as unsuitable decided against operation after they had realized the prospects of improvement. He assured the Section that the deafness in every case in the present series was, in his opinion, due primarily to otosclerosis.

It was quite true to say that otosclerosis was no longer an obscure disease. As was the case in many other diseases the cause was still not known, but the pathology was fully described. Moreover, the diagnosis of otosclerosis, except where it might be complicated by other otological disease, was not obscure, thanks to the constant clinical picture.

Owing to exigencies of space in the *Proceedings* the Honorary Editors are compelled to forgo publication of the following:

[*February* 3, 1950]

Speech Audiometry in the Assessment of Deafness. By Air Commodore E. D. D. DICKSON and F/Lt. D. L. CHADWICK.

[*March* 3, 1950]

DISCUSSION on **"Otitis Externa".**

Clinical and Pathological Observations on a Case of Leukæmia with Deafness and Vertigo. By Dr. C. S. HALLPIKE and Mr. M. SPENCER HARRISON.

[*May* 5, 1950]

DISCUSSION on **"Attic Suppuration".**

The Editor of the *Journal of Laryngology and Otology* has kindly agreed to publish all these contributions, with illustrations.

Section of Odontology

President—F. N. DOUBLEDAY, F.D.S., L.R.C.P., M.R.C.S.

[*January* 23, 1950]

Oral Pathology in Children

By Professor J. BOYES
University of Durham

THOSE who devote themselves to the study of oral pathology do not recognize the division of their subject into the oral pathology of adults and the oral pathology of children, but the clinician is aware of certain advantages in this classification and it is from the point of view of a clinician that this brief survey is presented.

There are only a few occasions when the advice of the dental surgeon is sought in connexion with the *newborn*. I think all of us regard it as a red-letter day when we are asked to see that pleasant curiosity, the infant born with teeth. I never stand by the cot of one of these infants without wondering if I am in the presence of one who in later life will be a national figure, for Louis XIV, Mirabeau, the anatomist Broca and Curius the defeater of Pyrrhus, to mention only a few, showed this abnormality. The prematurely erupted teeth should be extracted. If left they ulcerate the under surface of the tongue, to say nothing of the mother's nipple. Recently such a patient came under my observation. The mother did not wish the teeth to be removed but within three weeks there was a lingual ulcer and the tongue had so pressed upon the teeth that they became loose and were ultimately picked out with dressing forceps. This is not always the clinical course and I recall a patient in whom the teeth remained firm and to cure the very severe ulceration which had developed the teeth were removed. I know of a family in which this abnormality is hereditary; three generations have shown the condition. Nobody nowadays regards this early eruption as a sign of congenital syphilis.

Another condition for which the pædiatrician seeks early dental help is *micrognathia*. Because the infant's jaw is so small the tongue is forced to occupy part of the pharyngeal space and there are signs of respiratory obstruction. The principle of treatment is obvious and accepted by all; the mandible must be brought forward. All are agreed that it is most convenient to do this by means of a submandibular sling attached over the head. There the unanimity ends for each dentist who treats these children devises his own appliance, as a reference to the literature shows. A recent suggestion is that the jaw should be kept forward by a weight acting over a pulley. This is claimed to be eminently successful but I believe that the ingenuity of most dentists can overcome the problem in a less drastic way.

In former days the dentist's help was sought in the very early treatment of *cleft palate* and within a few days of birth the infant was using a suckling plate. I wonder if the spread of the present trend, in one or two centres of cleft-palate surgery, to delay operation till a much later age than at present will revive the demand for this appliance. Recently three cases of submucous or occult cleft came under observation. In one the defect was in the bone, in the second it was at the junction of the hard and soft palate and in the third it was in the soft palate and ended in a bifid uvula. Clefts of the face usually conform to the lines of junction of the various facial processes which appear during development.

True congenital defects of the *tongue* are not common. In former days the fear for a tongue-tied infant was considerable. In the few cases I have observed where this abnormal frænum had been left uncut there seemed to be no ill-effects. In the main, like the palate the tongue develops from two lateral parts which grow medially and the organ is completed by a small central mass posteriorly derived from the tuberculum impar. Clefts appear along the lines of fusion and abnormality from a bifid tip to the tongue with two lobes is possible. Excessive development of the portion from the tuberculum impar gives rise to the so-called second tongue on the dorsum of the main organ.

The cause of these malformations and defects has up till now remained inadequately explained and the science of teratology has been in the background as far as active and popular research is concerned. However, Gregg's observation of the association of congenital defects, especially cataracts and heart deformities, with the mother having an attack of rubella during the first three months of pregnancy, has stimulated enquiries once again into these distressing and handicapping states.

In the first months of infancy children are particularly prone to bacterial infections and apart from congenital and hereditary lesions oral pathology in infants is largely the pathology of infection and inflammation.

Stomatitis is common, especially the generalized acute streptococcal or staphylococcal type, and of course thrush in debilitated children. Two ulcerated conditions of the palate have been specially named, Bednar's aphthæ (bilateral ulceration of the hard palate) and the pseudodiphtheria of Epstein. It is worth while recalling the normal appearance of the infant's palate with the clinical swellings—the epithelial pearls. *Salivary gland inflammation* in the newborn is a troublesome condition. Bony swelling of the mandible and other bones is seen in a condition that seems to have been observed more frequently recently, the cortical hyperostosis of bone. Osteomyelitis occurs every now and again and in infants it is characteristically in the maxilla. Serious complications can occur with this condition especially when the pus enters the orbit. Thanks to penicillin and sulphonamide the terrors of these infections are now rapidly passing away.

The dentist is usually troubled by *teething* only in his role as a family man. However, teething is important and various general manifestations such as colds, bronchitis, and running noses are common occurrences at this time. Local penicillin would be helpful for those children whose gums become ulcerated and inflamed. The ideal would appear to be a penicillin lollipop but so far I cannot get any of the manufacturers to make one. I have made lollipops by freezing penicillin solution flavoured with peppermint round a stick. They are quite pleasant to suck but they melt rather quickly once outside the refrigerator and so cannot be dispensed for out-patients except in vacuum jars—which is not at the moment economical.

When the teeth erupt they may be normal or they may show some abnormality of form or size or colour. In the last group one sees every now and again the child with yellow teeth who has had icterus neonatorum.

Dental caries is one of the commonest diseases of children but cannot be treated at length in such a survey as this. Let it suffice then in this connexion to mention the first carious lesion liable to appear: this is on the labial surface of the upper central incisors. I have seen a number of children with active caries in these teeth before they are a year old, and many children lose their incisor teeth before all the temporary teeth have erupted. Some children are wearing dentures at the age of 3 years. I had hoped that the recently advocated ammonium ion tooth powder was going to help these children but so far I have been disappointed in the results.

In the first year of life most of the *neoplasms* are congenital. The benign nævus type of tumour is probably the commonest—the hæmangioma and the lymphangioma. The congenital epulis is rare and its pathology is inconstant. In the recorded cases it appears to have been seen only in female children and the only case that I have seen was also in a little girl. A common gum swelling on the other hand is the eruption cyst which is readily diagnosed by its blue colour and clinical features.

In considering oral disease in older children it is perhaps easier to consider the subject in terms of symptomatology.

The condition of the *tongue* can be extremely helpful, for example the typical strawberry tongue in scarlet fever and the dry, coated tongue in gastro-intestinal upsets. In infants no fur appears on the tongue till the filiform papillæ appear; these are absent at birth. Parents are occasionally worried about their children should they show lingua geographica, the symptomless wandering areas of desquamation. Nicotinic acid in the age proportion

of the adult dose of 150 mg. daily will usually clear the tongue. It is to be remembered that anæmia and nutritional deficiencies occur in children and consequently the smooth tongue can be seen in young patients. Of the *gum enlargements* found in children, the endocrine gingivitis is encountered from time to time in patients during the period of puberty. Mouth breathing is a frequent cause of hyperplastic gingivitis. The idiopathic fibromatosis gingivæ is rarely seen but the hyperplasia associated with epanutin is becoming more common as its use in epilepsy is increased. Epileptics frequently have ulcerated tongues or show healed scars as the result of biting their tongues. Sublingual ulcers are met in whooping cough as a result of trauma to the underside of the tongue during sickness.

Oral ulcers in children are clinically similar to the lesions in adults. Aphthous ulcers occur frequently in children. In one baby of 2 years there was a familial element, and his brother, mother and maternal grandmother all suffered from recurrent aphthous ulceration. The antihistamines give good results in the majority of cases of the recurrent type.

Until a year and a half ago I always taught that *tuberculous ulceration* in the mouth was secondary to a focus elsewhere, usually in the chest. However, since then I have had cause to alter this dogmatic point of view for, during this period, three patients have attended the Newcastle-upon-Tyne Dental Hospital suffering from primary tuberculous ulceration in the mouth. All children were carefully examined by my colleague, Dr. F. J. Miller, and no other focus was seen radiologically or discovered clinically. Under treatment with streptomycin the ulcers healed completely.

The oral stigmata in congenital *syphilis* have been so fully described elsewhere that they do not require mention here but as members of this Section we should remember that it was at a meeting of the Odontological Society that Sir Jonathan Hutchinson read his famous paper describing for the first time the teeth which bear his name. (*Trans. Odont. Soc. Gt. Brit.* (1858) **2**, 95).

The commonest *swelling* of the jaw is the abscess. An abscess of the mandibular first molar occasionally progresses to osteomyelitis of the mandible. To-day penicillin has altered the whole outlook towards this disease. The abnormality of the lower jaw as the result of arrested development, or the bird-face of temporomandibular joint ankylosis will, I believe, gradually disappear from our clinical experience. As in adults so in children—cysts cause a centrally expanding tumour of the jaw. The dentigerous cyst is the commonest and it is surprising how frequently a badly depressed but vertically placed tooth will erupt into good position once the cyst has been opened up. The traumatic cyst is interesting, being without epithelial lining. It is the result of the irritation and resorption of an intra-osseous hæmatoma and to open it is to cure it.

The appearance radiologically of bone destruction not related to the apices of teeth usually means malignancy. The clinical signs and symptoms of the *malignant neoplasms* of mesoblastic origin are well known. In view of the variation in sensitivity to radiotherapy I believe a biopsy should be performed to ascertain the best line of treatment. Recently a clinical sarcoma was proved histologically to be a plasmocytoma and vanished under deep X-ray therapy. A girl aged 14 had a swelling in the palate related to a badly broken-down upper first molar. The diagnosis of abscess seemed obvious and there was an area of rarefaction on the radiograph. Ten days after extraction a biopsy was performed and the histological diagnosis was osteoclastoma.

Another clinical sign of some importance in children's mouths is the *exfoliation of teeth*, not the physiological shedding of milk teeth but the loosening and extrusion of otherwise healthy teeth. Pink disease is probably the first condition that comes to mind when this clinical sign is presented. As Sir John Fraser showed, Hand-Schüller-Christian disease is another. From the dental point of view the fatty substance can look very like pus when a collection of it is liberated by the extraction of the loose teeth. Sometimes severe Vincent's ulceration will destroy the supporting tissues with loosening and exfoliation of the teeth. In one girl the teeth loosened at the age of 12. The most severely affected teeth were almost without any bone support whatever. There was no explanation, local and general examinations were negative except for some swelling of the gum and chronic inflammation.

A word or two to finish this brief survey about three general conditions of great dental importance, hæmophilia, congenital and acquired heart disease and bronchiectasis. In all children in this group prevention is better than cure and they must have constant dental supervision. For the past two years I have kept a register of all patients in this group that come my way; a system of three-monthly recall operates and caries is kept under control and the oral hygiene is supervised. This is the logical dental approach for these diseases and the anxiety of extractions for children with hæmophilia and heart disease no longer arises.

An Unusual Case of Locked Jaw.—J. F. LOCKWOOD, L.R.C.P., M.R.C.S., L.D.S.

The case I wish to place on record concerns a healthy man, aged 34, who awoke one morning to find his mandible locked in the closed position, in which it remained for ten days.

There was no history of mandibular disease or injury, nor of any recent cuts or abrasions.

On examination : $\frac{--654321 \mid 12345-78}{87-54321 \mid 123-56--}$ were standing.

Considerable calculus and marginal gingivitis were present. $\overline{8}|$ was very carious. No signs of acute inflammation were visible.

Efforts, by the patient and by me, produced opening of not more than 5 mm. and were painful.

X-rays of the temporomandibular joints were normal and showed the condyles to be in their rightful positions. Dental X-rays also were normal.

I began to suspect that the condition might be an hysterical one, but somewhat callous tickling of the soft palate and posterior pharyngeal wall failed to produce any change.

Then I noticed the presence of inferior protrusion of a degree sufficient to allow the lower canines to act as fulcra and to give the lower incisors room to overclose.

Further questioning based on this observation clarified the course of events. The patient had a habit of sleeping on his face with his chin resting on his forearm.

On the night in question, during the muscular relaxation of sleep, this attitude must have exerted upward pressure on the symphysis menti in such a way as to elevate the lower incisors and depress the mandibular condyles. This allowed one or both of the intra-articular discs to drop forward in the joint, so that, on waking, the return of muscular tone had trapped the disc or discs and locked the mandible in the closed position.

Acting on this hypothesis, I insinuated a Mason's gag on each side of the mouth and, after warning the patient, exerted gradually increasing pressure. Suddenly resistance disappeared. There was an audible click and the patient's hand flew to his left temporomandibular joint.

The following day the jaw was a little stiff first thing but the patient was able to enjoy his lunch. No further treatment was given.

Section of Neurology

President—JULIAN TAYLOR, C.B.E., M.S., F.R.C.S., F.R.A.C.S.

[*February* 2, 1950]

DISCUSSION ON FAINTS AND FITS

Sir Charles Symonds: The symptom common to fits and faints is loss of consciousness which, by definition, is of rapid onset and brief duration. By definition again the word "faint" commonly implies a loss of consciousness due to a temporary failure of the cerebral circulation of postural or reflex causation, not the result of heart disease. This definition would exclude from our consideration attacks caused by heart block or other cardiac disorder, and also those due to hypoglycæmia.

The word "fit" may be used to indicate that the loss of consciousness is attended by convulsions, or in a larger sense to include an attack or seizure of any kind that is epileptic. The wider meaning is clearly more appropriate. When, therefore, I speak of fits I shall mean epileptic attacks. The definition of epilepsy is not easy, but Hughlings Jackson's physiological concept of "occasional, sudden, excessive, rapid, and local discharges of grey matter" will serve—perhaps as well to-day as when it was first written. The confirmation of this hypothesis by the E.E.G. is indeed remarkable.

Having regard to these definitions there appears to be a distinction between fit and faint of fundamental importance. In the fit the disorder of function is at the onset local: it is somewhere—and it may be almost anywhere—*in* the brain. It is therefore to be expected that the symptoms of a fit will show great variety, depending upon the parts in which the discharge arises. That this is abundantly true is confirmed by clinical experience. The number of epileptic variants is legion. In the differential diagnosis it is often possible in a moment to decide that an attack is a fit, not a faint, by reason of its local sign, generally the aura described by the patient, sometimes the observation by others of particular movements or localized spasm. But there are many varieties of epileptic attack in which there is no clinical evidence of local origin, or at any rate none which distinguishes the attack absolutely from a faint. The aura is present in little more than a half of the attacks of idiopathic epilepsy. The spread of the discharge in a convulsive attack is often so rapid that the movements are at once generalized, and, even more important, the epileptic discharge may begin in those parts of the central nervous system which are also involved in fainting, a subject to which I shall return later.

By contrast with the local origin of the epileptic attack there is in a faint involvement of the brain as a whole. This does not, of course, mean that the brain is equally affected in all its parts at the same time by a particular degree of anoxia. There seems to be an order of susceptibility so that some parts give out before others. The retina, for example, fails early and so do the centres for postural tone. Dimness of vision and loss of equilibrium, therefore, happen in a faint before loss of consciousness. Thus in a faint, if the onset of anoxia is not too abrupt, there is a certain order of lost function which is characteristic. This is true of most faints but there are striking exceptions. In the disorders known as postural hypotension and carotid sinus syncope, which both fall within my definition, the onset of the faint may be abrupt, and this is also true in some cases of reflex—I mean emotional—fainting. The sudden onset of pallor, unconsciousness and falling then closely resembles the symptoms of a minor epileptic attack. The resemblance is even more striking when a faint is attended by convulsive movements. It is well known that these occur when cerebral anoxia is of sufficient degree and duration. They were recorded in 7% of a series of 362 faints in blood donors, whose symptoms were analysed in a Medical Research Council Report. There is no doubt that in a faint of reflex origin ventricular standstill may occur and when this happens loss of consciousness ensues within 5 to 10 seconds, and if the heart stops for 15 or 20 seconds there are convulsive movements.

This happened in a patient whose case I have reported elsewhere, a young man who was liable to faint at the sight or thought of illness or even when examined by a doctor. While serving in the Army he was referred to Captain Michael Ashby with the diagnosis of epilepsy confidently made by a medical officer who had witnessed an attack. While Captain Ashby was examining the patient he found that his pulse was beating about once in 3 seconds. I quote verbatim his note on what followed. "I had only time to take three more beats when it stopped completely, confirmed by auscultation, for 45 seconds, during which he had a fit, rolling eyes, rigidity, and a few convulsive movements. The pulse stopped before the fit by about 10 seconds." This was an extraordinarily complete observation of cardiac standstill in a faint. The electrocardiogram in this case was normal, and in a subsequent attack induced by Dr. Denis Williams while an E.E.G. was recorded there was no evidence of epileptic activity, so that I do not think there can be any doubt that this man's attacks were faints.

To return now to the subject of epileptic variants, there is little doubt that the discharge may be localized in those parts of the brain, wherever they may be, upon which the state of consciousness depends. The epileptic attack often consists of nothing else but a loss or disturbance of consciousness. When together with this loss there is loss of postural tone with falling, the symptoms of the attack are indistinguishable from those of a very sudden faint. But if there is loss of consciousness without falling I believe we are right in supposing the attack to be epileptic, for in a faint the two go together.

Other epileptic variants which may resemble faints are those which have their origin in visceral centres. There is little to be said on this subject which has not already been stated by Kinnier Wilson (1928) in his classic paper. Pallor, nausea, palpitation, and dizziness separately or in combination may usher in an epileptic attack, or may occur as its sole manifestations.

A woman aged 20 was referred to me for attacks which had begun three years before. She would suddenly feel sick and dizzy, with buzzing in her ears and inability to hear clearly. If possible she would lie down for a minute or two and would then feel quite well. She had never fallen and was positive that she did not lose her senses. Attacks had been witnessed by her parents. In one of them she was driving a car and said to her father "Oh, Daddy take the wheel". She turned pale and had recovered in a minute or two. On another occasion she was in the garden with her mother, said she felt faint, lay down on the grass for a minute, and then said she was all right. Later, however, she had an attack while alone in her bedroom, beginning in exactly the same way. She went to lie down, but lost her senses and was found unrousable twenty-five minutes later, having bitten her tongue and passed water. Enquiry revealed that for the past four years about three times a year she had woken in the morning with a headache, a sore tongue and sometimes a wet bed, feeling as if she had had a nightmare. Her subsequent story has been that of epileptic attacks, almost but not quite controlled by phenobarbitone and epanutin.

I think it fairly certain that the little attacks, which had been diagnosed as faints, were, in fact, epileptic.

One cannot mention visceral epileptic variants without referring to what Gowers (1907) called vaso-vagal attacks, a designation which has been widely misunderstood, mainly because the term vaso-vagal attack was much later used by Sir Thomas Lewis to describe fainting. Gowers used it for prolonged attacks comprising symptoms which he thought must be referable to a disturbance in the medullary centres. "The attacks", he states, "are never really brief, they seldom last less than ten minutes and more often continue for half an hour or more." The symptoms, according to Gowers, might include epigastric discomfort, respiratory distress, substernal discomfort, coldness, pallor and often a sense of impending death. These attacks are, I believe, quite rare and are not to be confused with so-called anxiety attacks. Kinnier Wilson in the paper already mentioned suggested that they were epileptic variants of visceral type, arguing that their extended nature was no insuperable obstacle in the way of acceptance of the hypothesis.

I have had under my care at nospital a woman who had attacks of this kind at infrequent intervals occurring during the day and lasting an hour, each being followed during the subsequent night by a major epileptic attack in her sleep.

It is of course the duration of vaso-vagal attacks which makes them unlike epilepsy but as an example of the manner in which a single visceral symptom of epilepsy may vary in duration I take substernal pain.

A man began to have attacks at the age of 29 and had half a dozen in the next five years. There was a sudden onset of what was described as a vice-like pain between chest and back, which rapidly increased in severity and after a few seconds he became unconscious for five minutes. In one attack he bit his tongue. Dr. Denis Williams on two occasions found an abnormality in the E.E.G. indicating a long-standing benign lesion of the left hemisphere.

A woman aged 37, who had previously suffered from migraine, had her first epileptic attack while at a theatre. It was preceded for an hour by a pain in her chest like indigestion. She then told her husband she was going to faint and had a fit in which she bit her tongue and passed water. On a subsequent occasion she experienced substernal pain all day, then felt a sudden rush from her stomach to her head (an epigastric aura) and had a fit.

The transition from this case to the next, which is an example of Gowers' vaso-vagal attacks, is I think easily followed.

A married woman, aged 25, began to have infrequent and causeless attacks which were all of the same kind. There was a sudden onset of substernal pain like toothache, everything started to swim, and her head sweated. She lay down and remained in this state (the substernal pain continuing) for about two hours with a feeling as if she were going to die. There were two more episodes of this kind in the next three months. Finally she had a more serious attack which brought her to see me. She was on holiday taking the air before breakfast when there was a sudden onset of substernal pain with sweating at the temples and sound coming and going. She just had time to say to her husband "Look out" before she fell unconscious. He stated that she was pale with stertorous breathing, stiff for the first quarter of a minute, them limp, and remained unresponsive for five minutes. She was confused for ten minutes afterwards and had no memory of being carried up to bed. After she recovered her senses she continued to have substernal pain for two hours and during this period felt giddy if she attempted to sit up. Neither I nor any of my colleagues could find anything wrong with this woman. E.C.G., E.E.G., fasting blood sugar, blood sugar curve, response of pulse-rate and blood pressure to posture and effort were all normal.

This has been a digression from the main theme of our discussion. Vaso-vagal attacks are not faints, nor are they in any ordinary sense fits, but the observations which I have put forward support Kinnier Wilson's argument that they may be epileptic.

Perhaps the most important distinction between faint and fit is the setting of the attack. Faints very rarely occur except in the erect posture. If an attack occurs after long unaccustomed standing, or as the result of sudden emotion or pain, in a hot and stuffy atmosphere, or after loss of blood, it may be presumed to be a faint unless there is evidence to the contrary. If it occurs without any of these causes it is probably a fit. Yet again, however, the distinction is imperfect. Epileptic attacks may be precipitated by various causes of which emotion is one. The malaise of infection may be another. In the following case both precipitants were evident.

The patient was a man of 61, whom I saw for an entirely different complaint, and the details which follow were obtained from his past history. He had as he said "fainted" on many occasions. The first was in his teens when he was taken to the doctor with influenza, the second at 19 after a cycle accident. He was not injured, but very much upset, and lost his senses suddenly fifteen minutes later. The next occasion was a year afterwards when he went to have a tooth out, and, feeling, as he said, in a blue funk, lost his senses and fell before getting into the dentist's chair. In this attack he passed urine. There was a similar episode at the dentist's a year later. Again he passed water. There were no more attacks precipitated by emotion, but on about a dozen occasions he had fainted at the onset of a febrile illness, influenza or bronchitis. The sequence was always the same. He would begin to yawn and continue yawning for ten to twenty minutes. If he could keep walking about this might end without further incident, but if he gave way and sat down his vision would suddenly become grey and he would lose his senses for a minute. In almost all these attacks he passed urine.

These attacks, I believe, were epileptic for two reasons. The first is the occurrence of involuntary micturition in nearly all the attacks. This may occur in a faint if the bladder happens to be full at the time, but its regular occurrence always suggests an epileptic discharge involving the centres for micturition. The second reason is the prodromal yawning, recognized by Gowers (1901) and again by Kinnier Wilson (1928) as a precursor of epileptic attacks. I have several examples of this in my own notes of undoubted epileptics.

There is next to be considered a rare but important group of patients who begin by having attacks in childhood or adolescence which we diagnose confidently as faints, but who go on to have attacks which we are sure are epileptic. The earlier attacks have the usual causes for a faint, but the liability appears excessive, the attacks are more frequent than usual and continue to a later age and when they have continued long enough we are not altogether surprised when we are confronted with the story of an attack this time without cause and characteristic of epilepsy. In these cases then we observe excessive liability to fainting followed by an excessive liability to epilepsy. The word excessive may be equally applied to both. Anyone may faint or have a fit with sufficient cause. Why do some persons have faints or fits with so little cause or no apparent cause? The answer in the case of the epileptic is that there are nervous centres which are unstable. This is the trigger mechanism for the attack. Of the causes that operate to pull the trigger we know very little. In the case of the fainter on the other hand we know a good deal about the causes that pull the trigger, and we know that when the trigger is pulled there is bradycardia or fall of blood pressure to explain the symptoms that follow. But where is the trigger itself? Probably in the central nervous system. Fainting in response to emotion clearly suggests this localization. Again in a faint which results from prolonged or unaccustomed standing what is it that gives way? Surely the reflex mechanisms responsible for maintenance of heart-rate and blood pressure, and where are these except in the central nervous system? In the syndrome of postural hypotension, which provides the extreme example of postural fainting, there is a good deal of evidence for the existence of a trigger mechanism at or near the hypothalamus (East and

Brigden, 1946). It seems probable, therefore, that for faints as well as fits an essential link in the chain of causation is an unstable nervous mechanism. If this be so it would not be surprising if we sometimes found both kinds of instability present in the same person. Nor I think would it be surprising to find that with the passage of time the instability responsible for fainting became less and that responsible for epilepsy greater. This kind of thing sometimes happens in persons who have migraine in their youth and as they grow older exchange it for epilepsy.

The carotid sinus syndrome is also of interest in relation to the occurrence of faints and fits in the same person. In this malady pressure upon the sinus, according to Ferris and others (1935), may produce faints, with bradycardia or fall of blood pressure sufficiently abrupt to cause loss of consciousness and sometimes convulsions: or it may cause these symptoms without any adequate cardiovascular derangement to explain them. Thus it would appear that the specific stimulus in this syndrome may produce either reflex fainting or reflex epilepsy.

The general trend of these remarks has been towards the conclusions, first, that there is no absolute means of distinguishing between a fit and a faint unless the attack can be observed in detail with estimations of pulse-rate and blood pressure before and during the episode, and second, that even though fits and faints may be clinically distinguishable they are closely related in their dependence upon the instability of nervous mechanisms.

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Dr. Denis Williams: "Familiar as fainting is, adequately as we seem to know it, there is much in it that we do not know. Our knowledge is enough to obscure our ignorance. The most obtrusive feature of complete cardiac syncope is the loss of consciousness which results, evidently due to the failure of the action of the heart which precedes and attends it. But the loss cannot be the direct effect of the cardiac failure, because consciousness is not the result of the circulation of the blood. To say this is to state an obvious truism, for the two are totally different in nature. The loss must be immediately due to a state of the nerve elements of the brain produced by the change in the circulation. We are apt to overlook this when we think of the process of fainting, but its recognition is of great importance because consciousness may be lost from other causes. It is the most common feature of the epileptic seizure. Not long ago it was thought to be a constant feature; without such loss an attack was said not to be epileptic. We now know that minor attacks are common in which consciousness is only dimmed: sometimes hardly a ruffle on its surface attends the sensation which constitutes the slightest form of attack. Still, in the pronounced form of each condition, in fainting and in epilepsy, loss of consciousness is a dominant feature. The fact is of practical importance in diagnosis, because it often makes their distinction difficult, and sometimes causes a mistake. For another reason, also, the loss of consciousness is important. We do not know in either malady the nature of the process in the nerve elements on which the symptom depends. We do not know whether it is the same in the two or is different. If we can trace any relation between the affections it will constitute some evidence on the question, evidence at least suggestive. For this reason also the study of fainting in relation to epilepsy is important."

Those words were written by Sir William Gowers over forty years ago, and they make it clear that we are discussing the problem in the same kind of way to-day as he did then.

Sir Charles Symonds has suggested that there may be a common link between epilepsy and syncope, although a precise distinction can normally be made between the two conditions upon clinical grounds. In considering any relationship between the two, it is of the utmost importance to keep such a distinction clear, for it is all too easy by elision to recognize a faint as a fit, and vice versa, and so seem to establish a relationship in any one case which does not, in fact, exist. Any experimental study of the relationship between epilepsy and fainting must be based on the certain recognition of an epileptic attack and a fainting attack as entities, and it is because of the failure to do so that so much work must be discarded. The criteria that Sir Charles Symonds has laid down are those which are readily acceptable to most of us, and such criteria should be employed in any experimental or statistical survey of the subject.

Kershman (1949) considered the relationship of "Syncope and Seizures". He took 114 patients who had a history of syncopal attacks or similar episodes without loss of consciousness. All of them had abnormal electroencephalograms between attacks but none of them had had a definite convulsive seizure. 65% had a diffuse dysrhythmia in the E.E.G. and Kershman concluded that "the form of the pathological E.E.G. abnormality and the character of the spells suggested a subcortical and probably hypothalamic origin for the attacks". He concluded that these "syncopal spells" were "a mild form of idiopathic epilepsy" and stated that "these spells were essentially the same as the vagal and vaso-vagal attacks described by Gowers, and the E.E.G. disturbances indicate that they are fundamentally epileptic in character".

At first glance all this might suggest that syncope is, as Kershman has suggested, a special if mild form of epilepsy. But the difficulty is that many of the cases included in his series clearly had epilepsy. Consider the first of his illustrative cases, that of a man who had an attack of unconsciousness while at breakfast, in which he suddenly felt a choking sensation, stood up and fell unconscious. He had urinary incontinence and recovered fifteen minutes later, weak and dizzy. In his next attack he was sitting, he had twitching of the lips and he was again unconscious. There is no doubt that this man was suffering from epilepsy and the absence of major convulsive movements does not in any way influence this fact.

This recent paper is quoted to emphasize the fact that no relationship between syncope and epilepsy must be claimed upon the results of statistical or experimental work which does not keep a clear distinction between loss of consciousness resulting from a change in cerebral blood flow (syncope) and that resulting from a primary change in cerebral activity (epilepsy). The clinical basis for this distinction is real.

Keeping clear the fact that there are, on clinical grounds, as well as upon the mechanisms responsible, distinctive differences between fits and faints, I would like to consider the evidences for a common bond between them. There are forms of syncope in which the mechanism of the loss of consciousness is so evident that it is hardly profitable to wonder whether an obscure cerebral mechanism is at work. Such are, for instance, the attacks of orthostatic hypotension resulting in loss of consciousness. There are others, however, in which there is a much closer affinity to epilepsy. I refer to reflex syncope caused by highly specific stimuli, often emotional in their background. The pattern of this disturbance is similar to that of some instances of so-called reflex epilepsy. We have already heard that habitual syncope and epilepsy may co-exist in the same patient, but when reflex syncope is considered the relationship between faints and fits occurring in the same subject may be close. The following are two cases which clearly illustrate this relationship.

Case 1.—An army officer aged 42 was undergoing dental treatment. 1% novocain had been injected, there was no pain and no apprehension. The dental surgeon said the patient suddenly went rigid, his pupils dilated, his eyes were open and he went into a tonic-clonic convulsion, with deviation of the head and body to the left. The convulsions lasted for 5 seconds, then he seemed normal. The patient said he suddenly felt ill, giddy, sweated profusely and then remembered no more until he found himself with his head in a basin. He was confused at that time. Afterwards he was cold and clammy, and the surgeon said that his pulse was thready. Important points are that the subject experienced no apprehension, or pain, that he was half lying throughout, and that the experience of the symptoms of fainting was momentary.

His past history showed that he had had the following kinds of attacks:

(1) In bed just before sleeping, about once a week he had a feeling of apprehension, thumping in the head, pounding of the heart, a hot clammy sensation and a feeling of pins and needles throughout the body. This disturbance seemed to last five minutes. It was never associated with loss of consciousness, incontinence or movement.

(2) In the daytime on sudden bending and rising he had typical postural hypotension with loss of consciousness.

(3) He had had repeated attacks of loss of consciousness in response to the sight of blood, accidents, or bomb casualties.

(4) On hot days, once or twice each summer, he had had attacks of unconsciousness which from the description were syncopal. The symptoms were similar to those of his attacks of orthostatic syncope, but the course of events was more rapid.

His only brother, a leader of a heavy rescue squad in the Civil Defence Services in London during the war, had never been upset by all kinds of horrible sights. Traumatic amputation of a finger did not greatly disturb him. He had lupus of the face and had to make frequent visits to hospital. He always had to be accompanied for treatment, because when he smelt the "smell of a hospital" he would fall to the ground unconscious with only the briefest warning. He might have time to say "I feel funny" then would fall, often hurting himself. He would have a tonic-clonic fit and be confused for a few minutes afterwards. He had never lost consciousness or even felt faint in response to any other stimulus.

The patient was normal on full examination. The E.C.G. and E.E.G. were both normal. Mechanical stimulation of the carotid sinus failed to produce any symptoms.

Here then is an example of a man having orthostatic and reflex syncope, hypnagogic disturbances and epileptic attacks in response to special circumstances, with a family history of epilepsy in response to a highly specific situation.

Case 2.—A young man of 19 hurt his hand slightly in machinery. He was having it dressed by a nurse when he suddenly fell off the chair in a tonic-clonic fit, which the nurse witnessed in detail. He was confused afterwards. He was not pale before the attack and he said he felt no great pain or apprehension while the wound was being dressed.

His past history showed that he was a high-grade defective, three years behind his age, whose physical development was normal. He had had no convulsions in infancy. When 8 he had a tonic-clonic attack after he had cut his finger, and after that he had six attacks at irregular intervals, each precipitated by sight of blood or injury to himself. In each he went pale then blue, fell to the ground and had convulsive movements. In one he was incontinent. He had no attacks of any sort in any other circumstances.

His mother, who was unstable emotionally, had periods of lack of emotional control when frustrated. At the height of her histrionic anger she would suddenly fall down, become cyanosed and have a tonic-clonic fit of short duration. She was usually incontinent in these attacks. The father, a brother and a sister were normal.

On examination, both the patient and his mother were normal. Their E.E.G.s were normal. In this case there was a maternal history of epilepsy in response to emotion, in a boy who had syncopal and epileptic attacks after physical injury.

There are innumerable instances of the presence of syncope and epilepsy in the same person, so that the point need not be stressed. The difficulty is to explain *why* the conditions should exist, and there are very many reasons why it is an over-simplification, and indeed a mistake, to presume that syncope is a minor and special form of epilepsy, as some would wish. It must be recalled that there are many cardiological causes of loss of consciousness, in which the mechanism at fault leads to a fall in cerebral blood pressure. For these such a point of view is clearly untenable.

I would now like to examine a small piece of evidence upon the nature of the common bond between the tendency to faint and the tendency to have fits. The electroencephalograms of four groups of subjects were examined. These groups were made up of large numbers of comparable cases, as in Table I. They comprised: (1) Patients referred for opinion who had had more than one fainting attack. These attacks, from the clinical description given and from the circumstances in which they had occurred, were, in my opinion, faints. In all there had been a fairly long period in which the patient was able to say to himself "I feel faint". This sense of impending loss of consciousness seems to be common to all but the most rapid forms of fainting (such as the Stokes-Adams attack). During this time there was usually a story of pallor, often sweating, coldness, and sometimes nausea. The patient often sought support, and if he failed to find it or to sit down, lost consciousness. In all these cases consciousness was lost. Whether or not convulsive movements followed such a chain of events was unimportant, for an epileptic attack often follows cerebral ischæmia. In none of these patients had there been a story of fits, however brief, which were not heralded by the symptoms of syncope or the circumstances which give rise to syncope.

(2) Patients with *grand mal* epilepsy, for which no cause had been found, and in whom fainting has not taken place—idiopathic epilepsy.

(3) Patients with a similar story in whom a head injury was thought to have been responsible—traumatic epilepsy.

(4) Normal men and women who had never lost consciousness.

All the subjects were adults, all serving in the Forces, and all were otherwise normal.

The electroencephalograms were divided upon (1) the existence of generalized abnormality of any kind, which placed the records beyond the limits of normal, which excluded at least 12% of the normal population (the standards employed have been described before, Williams, 1941), and (2) upon the presence of runs of abnormal fast waves (Figs. 1 and 2) in both frontal lobes. These disturbances were specially picked out for study because they had so often been seen to occur in patients in whom I had no doubt that syncope and not epilepsy was the correct diagnosis, upon the criteria already outlined.

The results of this division of the cases is shown in Table I.

TABLE I

		Electroencephalogram				
			Non-specific abnormality		Episodes of fast activity	
Diagnosis	No.	No.	%	No.	%
Syncope	68	21	31	13	19
Idiopathic *grand mal* ..	94	54	57	21	22
Traumatic epilepsy ..	68	49	72	14	21
Normal	70	11	16	3	4

FIG. 1.—Episodes of fast rhythms arising in both frontal lobes in a patient with repeated faints. The electroencephalogram is otherwise normal.

FIG. 2.—A normal electroencephalogram, similar to that in Fig. 1 except that there are no abnormal fast rhythms in the frontal lobes.

This shows that there is a significant increase in abnormality from normals to syncope and the epileptics, but it also shows that the proportion of those showing abnormal fast activity in the frontal lobes is the same in all the abnormal groups (about 20%), while it is only 4% in the normals.

Because of these results, members of the hospital staff were asked confidentially if they had ever had any attacks of any sort, and in 16 instances the subject had fainted more than once in his life, but had always been considered to be normal. None had had epileptic attacks. This small group of 16 otherwise normal fainters were in all other respects exactly comparable to the normal control group, none of whom had fainted more than once. In Table II it will be seen that the proportion with generalized dysrhythmia was the same in the two groups, whereas the proportion showing abnormal frontal fast activity was significantly higher in the small group of "fainters".

TABLE II

		Electroencephalogram				
			Non-specific abnormality		Episodes of fast activity	
Normal subjects	No.	No.	%	No.	%
Fainters	16	2	12·5	7	43·7
Others	70	11	15·7	3	4·3

Disturbances of an "epileptic" kind are probably absent from the subjects who faint in this series because of the care which had been taken to divide epilepsy from syncope, but even so there is an episodic disturbance of the kind so often seen in epileptics—particularly those suffering from *grand mal*—occurring in a proportion of people who faint, even though they felt normal at the time of the recording. It would be wrong to assume that this finding indicates that syncope and epilepsy are the same condition but it must indicate that a common factor exists in the mechanism of the two conditions.

The clinical experiences which have been recounted both by Sir Charles Symonds and myself would support the hypothesis that there is such a common factor, and this factor must surely reside in the cerebral hemispheres. It may well be that it consists of the kind of reaction of the hemispheres—the failure to maintain normal activity—in response to deleterious circumstances, whether these consist in changes arising in the hemispheres themselves or elsewhere in the body. That is to say that consciousness is more readily lost in these than in other subjects whether the cause is a fall in blood pressure or an abnormal discharge of neuronal activity in the brain. Certainly in epilepsy some people lose consciousness whenever an epileptic discharge occurs in the E.E.G., while others have numerous "larval attacks" in the E.E.G. without loss of consciousness (Williams, 1950). Certainly also in syncope some people lose consciousness more readily than others with a similar rate and extent of fall in blood pressure. There are at least three mechanisms responsible for the faint:

(1) The special response of the individual to specific circumstance, which may sometimes be a conditioned response to a previously emotional situation.

(2) The resulting disturbance in the cardiovascular regulating mechanisms.

(3) The consequent disturbance in cerebral activity, with loss of consciousness and other changes.

It is in the hemispheres that syncope and epilepsy have common ground, and the similar response of the hemispheres to different abnormal states may well be reflected in the common features seen in the E.E.G.

SUMMARY

Evidence is produced to support the view that one of the factors common to faints and fits is the failure o the individual to maintain consciousness in special circumstances. The view is expressed that although syncope and epilepsy may co-exist in the same family or the same individual, syncope is not a special form of epilepsy. The clinical and experimental knowledge that we have lends support to the view that, although the mechanisms responsible for faints and fits are different, they may occur in the same person because of a common factor in the hemispheres, reflected in the E.E.G. This factor may simply relate to a failure to maintain consciousness under the conditions which exist in the two disorders.

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Dr. Maurice Campbell: The identical word, syncope, is used for trivial fainting attacks and for a manner of death, and should, therefore, be banished from scientific discussion. It might be useful if it was recognized that syncope meant a sudden loss, and fainting a gradual loss of consciousness, but there is no such agreement and it would at present be wrong because syncope is by definition (O.E.D.) "a failure of the heart's action, resulting in loss of consciousness or sometimes in death". Fits are, of course, more often of cerebral origin, but not always: if loss of consciousness from anoxæmia lasts more than a certain time, the familiar sequence of events seen in any epileptiform attack will follow.

More accurate knowledge of attacks of unconsciousness will not be gained without more accurate descriptions and more precise terminology. The speed with which consciousness is lost is a fundamental distinction; and I suggest that the word tachy-apsychia should be used for sudden loss of consciousness, seen characteristically in most Stokes-Adams attacks or in epilepsy, and brady-apsychia for gradual loss of consciousness seen characteristically in most fainting attacks in young people. I am indebted to Mr. E. L. York of New College, Oxford, for the use of these words.

Loss of consciousness concerns the physiologist and neurologist even more than the cardiologist; but there is, perhaps, more knowledge of the provoking mechanism of unconsciousness in disorders of the heart than of the nervous system. The common factor in the former group is the production of cerebral anoxæmia—whether by change of rhythm, including ventricular standstill as in many Stokes-Adams attacks; by standstill of the heart as in a few fainting attacks, or during anæsthetics; by the combination of a slow heart and a fall of blood pressure or by one of these alone, as in most cases of fainting and of the carotid sinus syndrome; or by temporary arrest of the cerebral circulation by venous stasis or difficulty in auricular filling during violent spasms of coughing or after pulmonary embolism.

Broadly speaking, these various cardiovascular causes—and there are many more—can be divided into those where the cerebral circulation is arrested, often but not necessarily, by cardiac or ventricular standstill, and those where it is diminished (as in the severe fall of blood pressure after a large cardiac infarct or with a very rapid paroxysmal tachycardia) when the unconsciousness will generally be gradual.

As a rule, therefore, tachy-apsychia will mean sudden arrest, and brady-apsychia a gradual diminution of the cerebral circulation: there are, however exceptions, and of course, tachy-apsychia is often cerebral in origin. With arrest of the circulation there is greater danger of the heart failing to start again and so tachy-apsychia has, in general, a much graver prognosis than brady-apsychia.

A patient who has been unconscious can, as a rule, give the physician no direct indication as to whether the cause was cardiac or cerebral, and the decision may be difficult and may call for much knowledge and experience: the symptoms produced in either may be almost identical. It is, in particular, essential to be on familiar terms with epilepsy, in both its major and minor forms.

The duration of unconsciousness is of great importance in this connexion. A short attack, and this means one lasting less than two or perhaps five minutes, may be either cardiac or cerebral in origin. A long attack, lasting more than five or ten minutes, must be wholly or partly cerebral—partly when a short cardiac arrest starts the loss and produces anoxæmic changes in the cerebral cortex that prolong the unconsciousness.

Standstill of the heart or of the ventricle for from 5–10 seconds causes sudden loss of consciousness. Arrest of the cerebral circulation for from 5–10 seconds by a pressure cuff round the neck (Rossen *et al.*, 1943) causes sudden loss of consciousness, so this is further evidence that both act in the same way. Rossen *et al.* fixed a cuff round the neck that could be inflated to a pressure of 600 mm. Hg. In normal young men fixation of the eyeballs and blurring of vision were the first signs, nearly always within 5–7 sec. Loss of consciousness followed 1 sec. later, and the cuff was then released. Mild generalized convulsions followed but only lasted 6–8 sec. Consciousness was regained 4–10 sec. after the cuff was released. Longer periods of arrest of the cerebral circulation up to 100 sec. were produced in 11 patients with schizophrenia; all regained consciousness in 30–40 sec. and there were no after-effects.

In unconsciousness due to cerebral anoxæmia spasmodic movements or fits are dependent on the depth and duration of unconsciousness and not on its cause: they may, therefore, occur in attacks of all sorts. They follow 15–20 sec. after the arrest of circulation.

Arrest of the cerebral circulation for two minutes by standstill of the heart in disease or during anæsthesia or for 100 sec. in experiments on man is compatible with perfect recovery.

Standstill of the heart for 5 minutes is generally permanent, i.e. the patient is dead. In the rare cases where the heart starts again after longer than this, anoxæmia will have caused irreversible damage to the brain, especially to the cortex; and the first sign of this will often

be a longer period of unconsciousness. Where the cerebral arteries are diseased as in many cardiac cases and most Stokes-Adams attacks, a shorter period than five minutes may produce cerebral damage from which it is not possible to recover.

Standstill of the heart for more than two but less than five minutes will produce cerebral damage from which it may be possible to make a perfect recovery. The first sign of this cerebral damage may be a more prolonged period of unconsciousness. This means that even in a cardiac case that has been unconscious for many minutes, it is of great prognostic value to know when the circulation returns, i.e. when the heart starts beating. Ultimately this period of between two to five minutes may be defined more precisely though there will always be great danger about recovery in such cases. In clinical records of heart standstill periods of from 20 to 80 sec. are not often exceeded and these are well within the limits of complete recovery.

Table I shows the variety of conditions to be remembered and indicates whether tachy-apsychia or brady-apsychia is likely to be found.

TABLE I.—CARDIAC CAUSES OF LOSS OF CONSCIOUSNESS

I.—Standstill of heart, including long sino-auricular block. *Tachy-apsychia* if not preceded by IIA.
- A. Neurogenic (vagal)
  - (1) with normal heart.
  - (2) with heart disease.
- B. Myogenic, with heart disease.
- C. Anæsthesia.

II.—Slowing of heart with fall of B.P. *Brady-apsychia.*
- A. *Fainting attacks.*
- B. Carotid sinus syndrome.

A and B always neurogenic but may occur with heart disease.
- C. Postural hypotension
- D. Severe hæmorrhage } Fall of blood pressure only.

III.—Ventricular standstill. *Tachy-apsychia.*
- A. *Stokes-Adams attacks* (one form) (difficult if block paroxysmal). Always with heart disease.
- B. Neurogenic cases without previous heart block.

IV.—Tachycardia with changes of rhythm.
- A. Arrest of circulation. *Tachy-apsychia.*
  - (1) Paroxysmal ventricular fibrillation.
  - (2) Paroxysmal ventricular tachycardia.

  If with heart block 1 and 2 are *Stokes-Adams* attacks. And rarely from 3, 4 or 5 below.
- B. With slowing of circulation. *Brady-apsychia.*

  Some cases of 2 above.
  - (3) 1 : 1 auricular flutter.
  - (4) Onset of auricular fibrillation.*
  - (5) Paroxysmal auricular fibrillation or flutter.*
  - (6) Paroxysmal supraventricular tachycardia.*
  - (7) Repeated extrasystoles.*

* Only in those specially prone to fainting.

V.—Failure of the left ventricle.
- A. With cardiac infarction (which also causes other varieties).
- B. With angina pectoris.
- C. With aortic stenosis. Often with exertion and of serious import.
- D. With aortic regurgitation. Not serious unless syphilitic.
- E. With acute pulmonary œdema.

VI.—Failure to fill the left auricle.
- A. With pulmonary embolism.
- B. Tachy-apsychia from coughing (whooping cough, chronic bronchitis and alcoholics).

VII.—Failure to fill the right auricle.
- A. Fainting after unaccustomed exertion.
- B. A factor in ordinary faints, especially standing.
- C. ? postural hypotension.

VIII.—With cyanosis (asphyxia).
- A. With congenital heart disease.
- B. With Cheyne-Stokes respiration.

TABLE I (*continued*)

IX.—Unclassified.
- A. Hypertensive crises.
- B. With labyrinthine vertigo (falling common, unconsciousness rare).
- C. Gowers' syndrome (vaso-vagal).
- D. Cerebral effect of carotid sinus pressure without change of rate or fall of blood pressure.
- E. Cerebral embolism.
- F. Hypoglycæmic attacks.

[The speaker quoted examples of some of these varieties, especially with Stokes-Adams attacks, with aortic stenosis, with sudden attacks of coughing, and the many varieties with cardiac infarction.]

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Dr. M. N. Pai: Nearly every case of faints, fits and "blackouts" which does not respond to immediate treatment is likely to be referred to a psychiatrist on the assumption that treatment along psychiatric lines is indicated. On account of the socio-economic and medico-legal implications the psychiatrist who handles such a case is assuming a much greater responsibility than the neurologist unless he first satisfies himself as to the accuracy of the diagnosis. A subsequent diagnosis of epilepsy (made by the psychiatrist) may shatter the patient's faith in doctors, make him more hypochondriacal and induce in him a state of secondary anxiety which may again obscure the initial symptoms.

In the case of a member of the Forces a mistaken diagnosis of epilepsy may bring him some immediate advantages in the form of a discharge from the Forces and perhaps a high-percentage pension for life. The disadvantages are that he may be unnecessarily condemned to an indefinite period of anti-convulsant drug therapy with its occasional risk of intellectual deterioration and may also be precluded from obtaining employment commensurate with his intelligence and experience. There is also the stigma attached to epilepsy and considerable distress may be caused to his relatives.

On the other hand a hasty diagnosis of hysteria merely because the features of a fit do not conform to those of typical epilepsy may be tantamount to accusing the patient of evading his military obligations and civilian responsibilities. Sensible persons and their intelligent relatives resent such a diagnosis. If any Service person is invalided out on account of hysteria he may not only be denied a pension but may also have considerable difficulty in finding suitable employment. The rehabilitation of such persons is taxing the resources of psychiatrists, social workers and officers of the Ministry of Labour.

It is undesirable to diagnose epilepsy on the E.E.G. alone. For instance, in 1940–42 it was thought that an abnormal hyperpnœa response was evidence of epilepsy, quite a large number of patients suffering from hysterical fits and fainting attacks were diagnosed as epileptic and many were discharged from the Services on the basis of erroneous views about the E.E.G. The E.E.G. technique has improved considerably during the war and since about 1944 it has been recognized that an abnormal hyperpnœa response unrelated to the level of blood sugar has no significance.

Knowledge of this subject is now crystallizing and a positive E.E.G. may certainly help in clinching the diagnosis in any doubtful case. When a series of Service and civilian cases complaining of faints or fits were investigated by the E.E.G., it was found that a family history of fits, faints, psychoses and mental defect was commoner in those suffering from epilepsy than in those suffering from hysteria. The E.E.G. was also found useful in spotting epileptic equivalents. In one epileptic patient when the fits ceased there were for four years recurrent attacks of headaches and when these ceased there was periodic epistaxis for which no obvious cause could be found. The E.E.G. showed spikes, and administration of luminal controlled the epistaxis. In another patient with fainting attacks there was paroxysmal tachycardia and the E.E.G. showed paroxysmal outbursts diagnostic of epilepsy. In yet another patient when the fits were controlled there was sudden onset of compulsive-obsessional symptoms, e.g. washing hands; the E.E.G. showed the spike and wave pattern.

A diagnosis of epilepsy should be made with great caution and only after taking into consideration a reliable family history, details concerning previous health obtained from independent sources, careful observation of the fits and the E.E.G. During an attack the one positive physical sign which if present is pathognomonic of loss of consciousness and therefore in favour of a diagnosis of epilepsy is an extensor plantar reflex. Too much dependence on the E.E.G. alone may result in neglect of clinical observation and investiga-

tion with sometimes disastrous consequences. One of the patients sent to me as a case of hysterical faints had well-marked aortic regurgitation, another had advanced lymphosarcoma of the mediastinum and yet another patient was suffering from acute post-vaccinal encephalomyelitis.

Dr. W. Ritchie Russell emphasized that all brains can be made to discharge an epileptic fit, but in the so-called epileptic the threshold is low. In diagnosis there is no substitute for a careful record of what happened during a fit. Fit forms which can easily be posted to someone who saw the attack are of great value and should be widely used in out-patient practice. Elderly arteriosclerotic subjects sometimes have a fit while sleeping in a chair after a meal; this is preceded by pallor of the face and is probably due to cerebral anæmia. Those who suffer from postural syncope should be made to realize that they can prevent fainting if they at once stoop say to adjust their shoe-lace, of if they voluntarily contract strongly the abdominal and thigh muscles.

Dr. Sheila Sherlock: During fainting there is not only release of posterior pituitary extract but other evidence suggests that adrenaline is also liberated. Moreover, there is a re-distribution of blood in the body; the flow through the limb muscles increasing and that through the splanchnic area diminishing. All these events are apparently the effects of fainting. What is uncertain is the exact stimulus that sets this train of events in motion. For instance, is the abnormal rhythm which Dr. Denis Williams observed in the electroencephalogram a result of the faint rather than related to its causation?

Dr. Denis Williams, in reply to Dr. Sherlock: as the abnormal rhythms are present when the patient is in a normal state of consciousness they are presumably related to the basic cause of the instability, and are not an effect of the fainting.

Dr. Charles Baker: A not uncommon, but often unrecognized, cause of loss of consciousness is coughing. This was first described by Charcot in 1876 as laryngeal vertigo, with analogy to labyrinthine vertigo; and these cases have also been classified as laryngeal epilepsy. When my interest was aroused in this syndrome I had no difficulty in finding 9 cases; all were males, all were overweight, and chronic bronchitis and emphysema were common features. These features in the clinical picture were confirmed by a review of a fairly extensive literature, predominantly French (Baker, 1949). The mechanism both of faintness and loss of consciousness from coughing would appear to be a diminished flow of blood to the heart due to increased intrathoracic pressure when the glottis is closed; recent reports of cardiac catheterization during straining and coughing and positive pressure breathing tend to confirm this explanation. This is different from the carotid sinus syndrome. Emphysema would tend to augment the raised intrathoracic pressure owing to the absence of the elastic recoil of the lung; obesity would contribute to the diminished return of blood to the heart from the inferior vena cava by the loss of abdominal musculature; the occurrence in males is explained by the simple fact that men cough harder than women. The prognosis is good and the attacks are not dangerous though one man was reported as killing a pedestrian when he lost consciousness from coughing while driving his car; he was saved from a charge of manslaughter on the medical evidence.

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Section of Psychiatry

President—W. J. T. KIMBER, D.P.M.

[*January* 10, 1950]

JOINT MEETING WITH THE SOCIETY FOR THE STUDY OF ADDICTION

Biochemical Methods in the Treatment of Alcoholism, with Special Reference to Antabuse[1]

By ERIK JACOBSEN, M.D. (Copenhagen)

LIKE fire, alcohol is a good servant but a bad master. Why is it that for most of us alcohol is and remains a servant and why that for some of us alcohol becomes the master? There are two schools of thought: some explain this in terms of the victim's biochemical make-up, others explain it in terms of his psychological make-up. The truth is generally to be found mid-way between the two extremes, and even die-hard physiologists admit



FIG. 1.—Factors leading to alcoholism and consequences of alcoholism.

that to be effective, biochemical treatment of alcoholism must be accompanied and followed up by common-sense psychotherapy. In this paper, therefore, despite its biochemical title, due consideration will be given to the psychotherapeutic side of the problem.

We shall begin by trying to find something in common in the different points of view put forward about the ætiology of alcoholic addiction. Fig. 1 shows on the left the factors leading to alcoholism, and on the right its consequences. Free access to alcohol is of course essential for the development of alcoholism, but only in conjunction with other factors present either in the patient's milieu (here called external factors), or in the patient himself

[1]From the Biological Laboratories of Medicinalco Ltd., Copenhagen S.

(the internal factors). Among the external factors, bad social conditions, such as seen in slums, and poor farming districts, family dissension, financial and other personal worries may directly or indirectly lead to alcoholism. Drinking among one's friends, colleagues or mates are other external factors to be considered.

In addition to this, the patient himself must in some way or other be disposed to alcohol addiction, but it is difficult to reach agreement about which factor or factors are essential. Some workers lay stress on anxiety or Freudian complexes, others on a psychopathic constitution: a lack of ability to adapt oneself to life. In the psychiatric literature we find many attempts to describe what constitutional factors alcoholics have in common, but these efforts have not led to clear results. Some people acquire a compulsion to continue drinking when they have taken a certain amount of alcohol. Such persons run a great risk of becoming alcoholics, especially when the necessary amount of alcohol (here called the "critical dose") is relatively small. Other workers are inclined to attribute alcoholism to biochemical or metabolic disturbances (for instance in the carbohydrate or the citric acid metabolism), but their views are not accepted by all.

Probably there is no single cause of alcoholism, but a series of causes varying from patient to patient. In some cases the external factors predominate while internal constitutional factors play no more than a minor role, in other cases the predominance of internal factors (whatever they may be) cannot be denied, but even here the combination of factors may vary from case to case.

Once developed, alcoholism leads to effects which come under these three groups: social decline, medical effects, and psychological and metabolic effects. Some of these, of course, aggravate the existing alcoholism. The social decline reinforces the already existing external factors which originally led to alcoholism. The psychological effects may also augment the trend towards alcoholism, for instance, neuroses may develop which are drowned in more alcohol. Needless to say, the resulting moral deterioration does not improve the situation, and lastly it is well known that the alcoholized organism craves for more alcohol. Owing to such vicious circles, once started, the addiction develops steadily. Sometimes the factors which originally lead to alcoholism become of minor importance in the maintenance of addiction compared with the vicious circle itself.

Prophylactic and therapeutic measures can be taken against alcoholism at the three main points marked by the letters A, B, and C in Fig. 1. Table I shows what forms of treatment may be directed against these.

TABLE I.—EXAMPLES OF THERAPEUTIC MEASURES WHICH CAN BE TAKEN IN THE TREATMENT OF ALCOHOLISM

A. *Adjusting "internal factors"*
- Explanation of the character of the addiction.
- Psychotherapy of neuroses.
- Group therapy such as "Alcoholics Anonymous".
- Religious influence through Church, Salvation Army, &c.
- Moral influence through Temperance Societies.
- Moral influence by threat of legal procedures.
- Medical treatment of metabolic disturbances (if present).
- Treatment of compulsory craving (if present) by insulin-glucose or alcohol intravenously, &c.
- Treatment of anxiety with apomorphine. After Dent [20].

B. *Withdrawal of alcohol*
- Segregation in mental hospital.
- Aversion treatment with emetin.
- Hypnosis.
- Antabuse.

C. *Adjusting "external factors"*
- Regulating patient's family life and home conditions.
- Educating patient's relatives.
- Helping to improve patient's social position.
- Adjusting patient's economic conditions.
- Removing patient from a heavily "alcoholized" milieu.

Certain treatments attempt to deprive the patient of alcohol (*see* B in Fig. 1, and the table), and quite a number of physicians believe that this is sufficient in itself. Experience, however, shows that deprivation of alcohol will produce temporary abstinence only, from which the patient sooner or later relapses. Therefore all factors leading to alcoholism must be treated—internal factors by suitable psychotherapy (often the most difficult task in the whole treatment), external factors by reorganizing the patient's life. In spite of this, the importance

of withdrawing alcohol must not be underestimated, as this may break the vicious circle maintaining the alcoholism.

However, it is difficult to find a method of withdrawal that will *effectively* support the other forms of treatment required. Thus, although committing the patient to a mental hospital or a clinic for a few months may give excellent opportunities for restoring him physically and mentally, the important social rehabilitation must wait until the patient is discharged, and valuable time is thus lost. On the other hand, if the patient is discharged too soon, supervision may be difficult to achieve. Other methods such as conditioned reflex treatment or suggestion allow the simultaneous attack by psychotherapeutic and social measures, but unfortunately not all patients respond satisfactorily. Moreover these forms of therapy are generally very elaborate and sometimes very unpleasant to the patients.

A few years ago it was discovered that an organic sulphur compound—tetraethylthiuramdisulphide—now known as *Antabuse*, sensitizes the system to alcohol, so that even small doses of alcohol result in a very intense discomfort, while no symptoms are felt so long as the person premedicated with Antabuse takes no alcohol. The discomfort is so intense that it will prevent an overwhelming majority from continued drinking. It was thought that the use of this drug would be helpful in the treatment of alcoholics, and about two years ago the clinical experiments were started.

This principle of treatment has, so far as we know, never before been applied in the treatment of alcoholism. However, the introduction of a new drug creates a series of problems which can be solved only by experiment and observation. Experiments and observations have now been carried out to such an extent that we begin to have some ideas of the general background for this special form of treatment.

Antabuse in itself is relatively innocuous, though side-effects, such as drowsiness, tiredness and indigestion may occur. In general, such side-effects are without practical importance, and can be kept under control by adjusting the dosage.

If alcohol, even in small doses, is taken by a patient premedicated with Antabuse, characteristic objective and subjective symptoms develop [1–8]. The reaction sets in five to fifteen minutes after taking alcohol. It begins with a feeling of heat in the face, then leads to intensive vasodilatation in face and neck, making the whole area purple-red, and the pulse rate rises sharply. All this is accompanied by intense discomfort: palpitations, dyspnœa, a constrictive feeling in the neck as though "the collar has become too tight", nausea and vomiting may commonly occur and on the top of it a highly disagreeable feeling, difficult to describe, of "premature hangover" will arise.

In the majority of the cases this Antabuse-alcohol reaction (though very disagreeable to the patient) is transient and without alarming objective symptoms, though rather a steep fall in blood pressure has occasionally been observed. There have been reported cases of death in apparently sound individuals [9] after a "test drink" (which will be described later) but one or two accidents among more than 20,000 patients treated with Antabuse shows that mishaps are not unduly frequent. Detailed description of the effect on respiration is given by Asmussen *et al.* [10] and of the effect on the heart by Raby and Lauritsen [11].

The biochemical mechanism of the Antabuse-alcohol reaction is on the whole clear since Antabuse inhibits the aldehyde oxidase of the liver [12]. The metabolism of acetaldehyde—a step in the oxidation of alcohol—is thus delayed and a high concentration of acetaldehyde is formed by the liver [13, 14, 15]. In consequence the blood acetaldehyde concentration rises, and this "acetaldehydeæmia" is responsible for the symptoms experienced by the Antabuse-treated patient after taking alcohol [16].

In the first 200 patients treated by Dr. Martensen-Larsen who was the first to develop the practical use of Antabuse[1], the general lines of treatment are as follows:

The patient is first kept off all alcohol for a few days so that there is no alcohol in his system when Antabuse is given, and then follows medication with 0·5 to 1 gramme Antabuse daily. After two or three days he is given the "test drink" of a small dose of alcohol (equivalent to 10–20 c.c. of absolute alcohol) in the presence of the doctor, so as to bring home to him the new and disagreeable effect of alcohol. After this test drink, the Antabuse dose is adjusted according to the severity of the reaction shown, and to the nature of the side-effects observed. The maintenance dose is continued for some months according to the individual requirements of the patient.

In addition to this, psychotherapeutic and social measures are instituted on the following lines:

The nature of alcohol addiction is explained to the patient, and he is told that his constitution is such that he must avoid alcohol as one avoids poison. During several consultations the patient's personal problems are discussed and he is given every psychotherapeutic

[1]All patients consulting Dr. Martensen-Larsen for alcoholism were treated with Antabuse, and a description of these patients on an earlier stage is given by Martensen-Larsen [17, 18] and by Jacobsen and Martensen-Larsen [19].

help to solve these problems. Since group therapy has proved useful, patients are encouraged to assist one another, and this often gives them self-confidence enough to overcome the inferiority complexes that are so characteristic of alcoholics. To augment such group therapy, an association on the lines of Alcoholics Anonymous has been formed for after-treatment. Here ex-patients are given opportunities to bridge the gaps that remain in their lives after renouncing alcohol, and the ups and downs of their fellows serve as encouragement and warning to them. Lastly, a guardian is appointed to the patient, preferably wife, friend, or employer, who watches over the treatment and is instructed to report to the doctor if anything should go wrong.

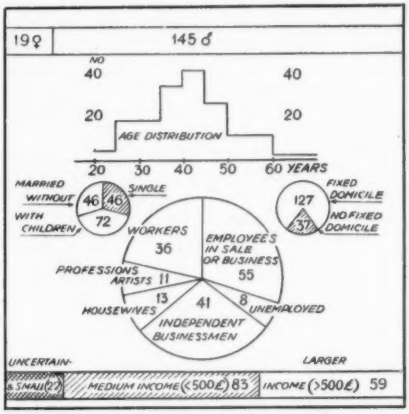


FIG. 2.—The first 164 patients treated with Antabuse grouped according to social background, &c.

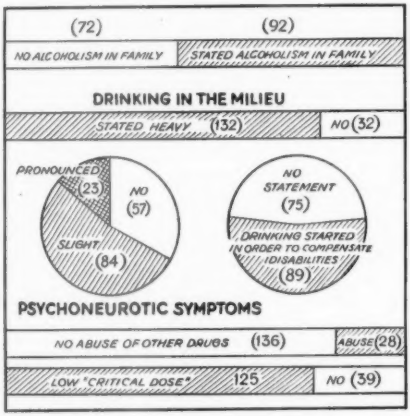


FIG. 3.—Some factors leading to alcoholism in the first 164 patients treated with Antabuse.

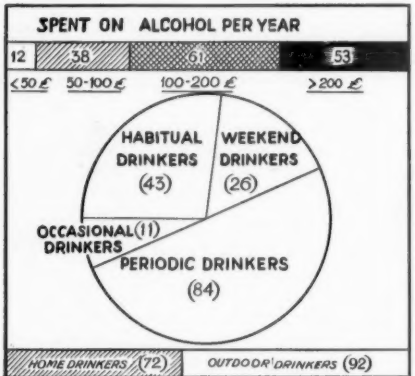


FIG. 4.—Alcoholic habits of the first 164 patients treated with Antabuse.

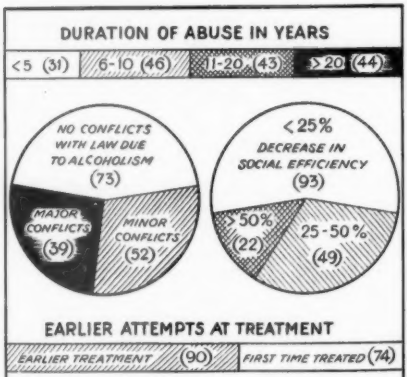


FIG. 5.—Same 164 patients: duration of abuse in years, patients' decline in social efficiency, conflicts with the law, &c.

Of these 200 patients now to be reviewed, 17 were only seen for such a short time that proper treatment could not be instituted. Another 16 disappeared from the doctor's view, and 3 died (from cerebral hæmorrhage, accident (while sober) and suicide). Of the remaining 164 patients, 112 were observed for twelve months, and 42 for nine months.

Fig. 2 gives a general idea of this series according to age, income, employment, marital status, and so on. Some factors leading to alcoholism are shown in Fig. 3. As already stated,

the "critical dose" is the dose of alcohol sufficient to drive the patient to further recourse to alcohol. In most cases the critical dose was about 2 or 3 drinks (equivalent to 10–20 c.c. of absolute alcohol), but even 5 drinks may be regarded as a low critical dose, and this may have some influence upon the development of the addiction. Fig. 4 shows the amount of money spent on alcohol during a year, and whether the patients were regarded as habitual, periodic or week-end drinkers. Fig. 5 shows the duration of abuse in years, the patients' decline in social efficiency, and their conflicts with the law.

The results of treatment are summed up in Fig. 6. This figure shows the results in the 112 patients treated for twelve months.

The results nine months after commencing treatment were analysed statistically, the patients being grouped as shown in Figs. 2—5. Younger patients, patients with small decrease in social efficiency, and patients with no or slight psychoneurotic symptoms showed somewhat better results than the rest. Apart from this no significant difference in the results was found from group to group.

Regarding the role of therapeutic measures, only the regularity of medication can be analysed. This, however, is of paramount importance. Fig. 7 shows the state of affairs

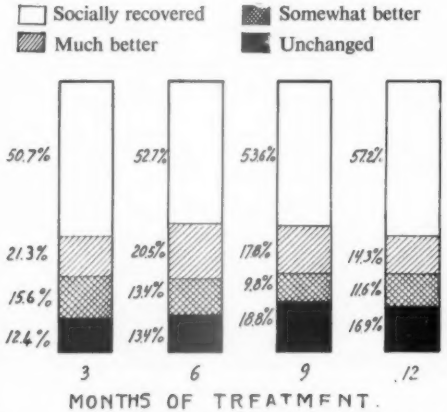


FIG. 6.—Synopsis of results of one year's treatment with Antabuse in the first 112 patients.

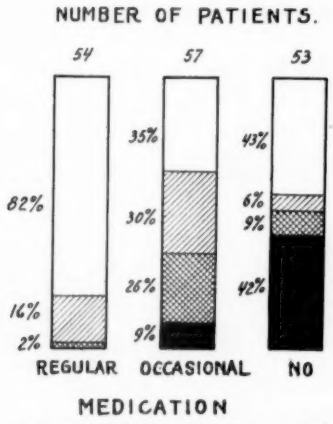


FIG. 7.—Results after six months' treatment, analysed according to regularity of medication.

at the end of six months according to regularity of medication. 82% of the patients who took Antabuse regularly during the six months may be regarded as socially recovered. The third column shows that patients who stopped taking Antabuse before the six months were up fall into two main groups, those recovered socially and those unimproved. The unimproved are patients who lost interest in the treatment and discontinued their medication. The socially recovered are patients who took Antabuse for some months, regained their mental and social stability and were able to keep off alcohol without further recourse to Antabuse. The second column shows results in patients who took Antabuse only occasionally, and the groups "much improved" and "somewhat improved" dominate the picture here. These patients take Antabuse for a while, then get tired of abstinence, stop taking their tablets, start to drink, and when they or their families find they have drunk enough, resume medication and remain sober for periods of varying length. These patients are of course a nuisance to the therapist since they have not understood the aim of treatment.

As in every treatment of alcoholism, the interest the patient takes in his treatment is of the greatest prognostic importance. As Fig. 8 shows, patients who showed lack of interest by discontinuing their medication in less than two months had done much worse, when reviewed after nine months, than those who continued medication for at least two months.

A further analysis shows that these latter patients more willingly submitted themselves to other therapeutic measures, were more co-operative in psychotherapy, had joined the

A.A. groups, and so on. Of equal importance is the attitude of the patient's relatives. In Fig. 9 there is a considerable difference between the results in patients with understanding and co-operative relatives, and in those whose relatives did not understand the treatment or were ignorant of its aim.

Early in the clinical experiments it became clear that Antabuse in itself is not a cure for alcoholism but only an adjuvant to be used in conjunction with other available methods. Antabuse given alone will achieve abstinence only as long as the patient has the energy to take his tablets—hardly longer than the periods of abstinence so solemnly promised by any alcoholic.

For several reasons, clandestine medication by Antabuse is absolutely contra-indicated, however tempting it may be. Firstly, if the patient is not warned about the effect that alcohol will now have upon him after the taking of Antabuse, he may have a serious reaction should he happen to drink a large quantity before the symptoms have had time to develop. Secondly, he will readily discover what has been done, and will distrust his family and his doctor accordingly and it will be difficult to give proper treatment later on. Lastly, it cannot be left to the discretion of wives or other unqualified persons whether or not treatment for addiction is indicated. Therefore Antabuse cannot be used except with the patient's full consent and comprehension.

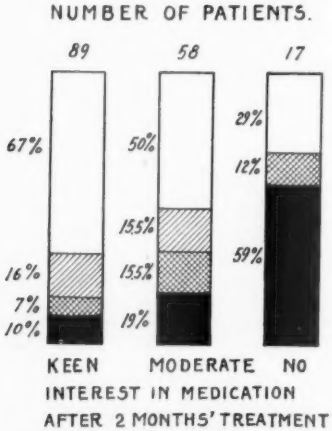


FIG. 8.—Showing results after nine months' treatment in patients grouped according to their willingness to take the tablets after two months' treatment.

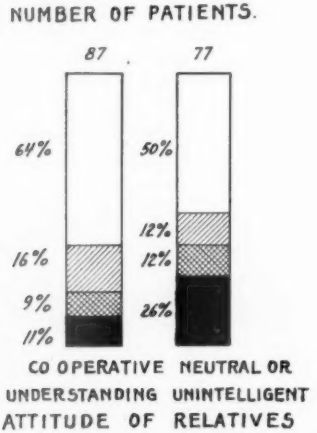


FIG. 9.—Showing results after nine months' treatment in patients grouped according to attitude of their relatives.

As with every treatment for alcoholism, the first aim must be to re-educate the patient and help him to lead an alcohol-free life. Antabuse must be regarded as a chemical confinement, and a wall established between alcohol and the patient, so long as he takes his tablets. This wall cannot be expected to stand indefinitely, but while it does all available psychotherapeutic measures must be applied. These should be maintained on three lines: (i) The patient must be encouraged to continue medication for a sufficiently long time; (ii) the gap which is left in the patient's life after he has stopped drinking must be filled by new interests. This can be extremely difficult, especially in elderly people, and it is probable that the poor results with these are largely due to this; (iii) the still existing mental disabilities which led to the addiction must be treated.

Enforced abstinence by means of Antabuse gives good insight into the significance of the factors leading to alcoholism, shown in Fig. 1. The vicious circles being interrupted, a high percentage of patients get their economic conditions and family conflicts settled in astonishingly short time, often in less than a month. In its turn this fact has the psychological effect of encouraging the patient a great deal. As regards the psychological effects of alcoholism, two factors appear to dominate the picture. In the first place there is the feeling of shame which is probably experienced by most alcoholics. Psychotherapy must therefore be mainly

directed against this. Secondly, there is the fear of alcohol intake, and of its consequences. Many patients have several times in vain tried to stop taking alcohol, and with every unsuccessful attempt self-confidence suffers and the fear increases. When, however, the patient discovers that by means of Antabuse he is unable to take alcohol, this fear is replaced by a feeling of happiness and confidence never known before. An American patient expressed this feeling thus: "At my earlier attempts to be abstinent I had to spend all my energy merely to avoid the temptation of drinking, now I can use it on items which are much more important." This stage is reached early in the treatment and lasts for about two to three months. The therapist must never be deceived by this early, almost over-successful development, for the patient will sooner or later discover that even life without alcohol has its problems, or the newly acquired self-confidence may lead him to stop his medication too soon. In both cases he will be tempted to drink, and thus relapses. For this reason the third and fourth months of treatment are a critical time for many patients, and it is important to have a guardian who immediately reports developments to the doctor so that medication can be resumed before serious damage is done. Several patients have had one or a few short relapses before the situation became stabilized. It is, of course, difficult to know how long to continue medication. Fig. 10 shows the duration of medication in 34 patients who were observed

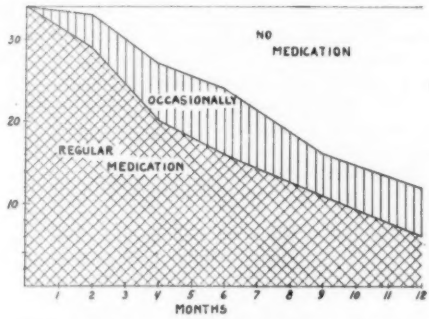


FIG. 10.—Diagram showing constancy of medication during twelve months' observation period in 34 patients socially recovered.

for more than one year and who recovered socially during that time. Great individual variation is seen. Some patients stopped taking Antabuse after a few months, while others continued to take it for more than a year. The average seems to lie between six and nine months.

We must now consider to what extent the psychological complexes or neuroses persist which originally led to alcoholism. Some cases offer difficult problems after the withdrawal of alcohol and the suicide of one patient in this series probably shows up such an unsolved problem. In most cases, however, the original conflicts seem to fade when the addiction is brought to an end, and thus the psychological picture of the addiction has been dominated by factors introduced by the addiction itself. The majority of the patients had the above-mentioned low critical dose for alcohol. Presumably their drinking was originally started by minor disabilities to which many non-alcoholics may also respond by drinking. But unlike normal persons alcoholics are not able to stop drinking when they have got over the critical dose. They continue drinking and develop an addiction with all its mental, psychological and social consequences.

In conclusion it may be admitted that the number of well-observed patients is still too small and the observation time too short to allow more than tentative conclusions about the therapeutic value of Antabuse.

The therapy must of course be individual. Results depend to a high degree on the teamwork of doctors and social workers and on the facilities for group therapy. Within this framework Antabuse plays a role, but it must be understood that the results obtained only in part depend on the drug, and are as good as the psychological and social therapy used.

For this reason we prefer not to speak of Antabuse therapy, but of treatment of alcoholism with the help of Antabuse. While it is true that Antabuse is useful in the therapy of addiction, we agree with the Danish psychiatrist who said that the introduction of Antabuse has not made the treatment any easier, though it may have made it more encouraging.

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Section of Comparative Medicine

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[*February* 15, 1950]

DISCUSSION ON THE MECHANISMS OF DISEASE PRODUCTION BY ECTOPARASITES

Mr. H. E. Harbour: In considering this subject one's mind naturally leaps to the various problems associated with the transmission of disease microbes by blood-sucking arthropods but the subject really covers a much wider field. We have to consider not only the various ways in which ectoparasites contrive to transmit various pathogens to their hosts but also the ways in which certain of the ectoparasites themselves produce disease by the direct effect which they have on their hosts. It is not always appreciated that the emaciation and anæmia produced in an animal by a very heavy infestation of external parasites of one kind or another is just as much a disease as the emaciation which may be the main clinical symptom of infection with some bacterial pathogen.

Melophagus ovinus.—The sheep ked is a wingless fly whose whole structure, like other members of the Pupipara, has been modified to meet the demands of ectoparasitic life. It lives its whole life on the sheep and feeds by sucking blood. It is a very benign parasite and, for the most part, does no harm, but it is very active, constantly on the move and frequently feeding, and its presence in large numbers leads to intense irritation causing the host sheep to spend much of its time scratching and rubbing when it should be quietly feeding. The result is unthriftiness and loss of weight and a marked disturbance in wool growth. The ked is found all over the world wherever sheep are kept and is an example of a reasonably benign parasite, well adapted to its parasitic life, and its habit is probably very ancient in the evolutionary scale. Incidentally the ked transmits a trypanosome (*Trypanosoma melophagium*) but this is an even more perfectly behaved parasite and apparently does no harm to its host at all [1].

Lice.—Biting lice produce their effect on the host simply by the irritation they cause in moving rapidly about over the surface of the skin, feeding on skin debris at the base of the wool, hair or feathers. In domestic animals heavy infestations of biting lice can cause considerable trouble in much the same way as the ked.

When biting and sucking lice are present in very large numbers they may produce, in cattle, a considerable degree of direct damage to the skin, leading to the oozing of exudates, the thickening of skin and the formation of crusts bearing a strong resemblance to the lesions produced by the scab acari. In man sucking lice may produce abnormalities of various kinds. Small papules frequently develop at the site of the bite and sensitization often occurs with further infestation leading to urticaria or general papular eruptions. These are the direct responses to the irritation caused by the bite of the lice, presumably through some irritant property of their saliva, and the allergic phenomena following sensi-

tization. Very heavy infestations have been said to give rise to symptoms of headache, drowsiness, pains in joints, a rash resembling that of German measles and a slight rise in temperature, and these symptoms have been thought to be due to the inoculation of some toxic substance with the saliva.

Apart from these results there may be secondary skin infections of various kinds and long-continued infestation may lead to thickening and pigmentation of the skin, the so-called "vagabond's disease" [2].

Mange acari.—Parasites which give rise to a more well-defined disease are the mange acari which cause scabies in man and the various forms of mange in the domestic animals. Here again the diseases are the result of direct mechanical damage to the skin and possibly also to the damaging effect of toxic secretions. In the sarcoptic group the mites burrow in the epidermis and as they feed on the tissues they deposit fæcal pellets which are thought to cause the formation of skin vesicles and to cause intense pruritis. Scratching then causes weeping of the lesion and entry of pyogenic organisms produces the secondary complications.

The psoroptic mites, which do not burrow, puncture the epidermis and stimulate a local reaction in the form of a small vesicle. This bursts and the exudate spreads out on the surface and coagulates. This results in the formation of a thick crust which dries and hardens and the wool or hair becomes loose and falls out. The mites then migrate to the edge of the lesion and feed there so that the scab is constantly extending. The irritation caused by the movements of the mites, and possibly also by toxic secretions, is intense and the sheep or other animal rapidly becomes emaciated.

Ticks.—The direct damage caused by ticks may be considerable but with a few exceptions is only serious when infestations are heavy. Generally speaking, they do not cause much irritation when actually attaching but the presence of the mouth parts embedded in the skin often produces an inflammatory reaction with local hyperæmia, œdema, and hæmorrhage, and tick bites often become secondarily infected with pyogenic organisms. When infestations are large the effect on the host may be very great and will be characterized by general unthriftiness and anæmia, while in dairy cattle there may be substantial losses in milk yield. Anæmia has been produced experimentally in rabbits by infestations of *Dermacentor andersoni* [3] and anæmias undoubtedly occur in heavy tick infestations in nature.

Apart from these effects the bite of some ticks, particularly some of the Argasids, may be very unpleasant and cause markedly painful swellings which may persist for days.

The tropical warble fly.—Another type of parasite which does direct damage to the animal is the fly which lays its eggs on the human or animal host or contrives in some way to have its eggs transported to the host where the larvæ burrow into the skin to feed and where they produce damage of various kinds. The tropical warble fly, *Dermatobia hominis*, is a pest of very serious economic importance to the cattle industry from Central Mexico to the Argentine, apart from its occasional nuisance to man himself. This fly employs the ingenious trick of attaching batches of 15–20 eggs to the underside of the abdomen of various mosquitoes and flies. The eggs hatch after a few days and when the carrier fly is visiting a warm-blooded host the larvæ emerge and quickly penetrate the skin. Here they feed, grow, and moult twice; they produce a good deal of local tissue damage and the toxic by-products of the larva produce pain and intolerable pruritis. There may be an associated lymphangitis in human cases. The pest causes very severe damage to the hides of cattle in these areas as very large numbers of the larvæ may be present at one time. In the Northern Hemisphere the warble flies are troublesome in cattle. In their case their effects are produced by the migration of the larvæ through the body, as well as from the direct damage to the hide caused by the presence of the "warbles" in the skin of the back.

Flies which produce myiasis.—Another group of flies which is of great importance is the group which produces the various types of myiasis. MacLeod [4] recognized three types: Type A is attracted by the odour of fresh tissue and strikes wounds; type B is attracted both by fresh and decomposing tissue and strikes both wounds and unbroken skin; type C is attracted by odours of decomposition only and can attack living animals only where there is already existing myiasis or diseased tissue. MacLeod regards these as simple variations of the carrion-infesting habit.

An example of the first type is *Cochliomyia hominivorax*, the so-called screw-worm which does so much damage to cattle in both North and South America. Maggot-fly strike of sheep is caused by the second and possibly also the third type of fly. This is a disease of very serious economic importance to sheep farmers in Britain and Australia and it has become increasingly important in South Africa and is quite troublesome in New Zealand. The

development of the myiasis habit by carrion-infesting flies is very interesting. At our own doorstep we see a marked contrast since in Britain blowfly strike due to *Lucilia sericata* is a very serious pest, yet though this fly occurs just across the Channel in France it has never developed to any great extent the myiasis habit and maggot-fly strike is not a serious problem in France, or indeed on the Continent.

The mechanism of disease production by these flies is twofold. In the first place they must be attracted to the sheep in order to lay their eggs and in the second place the larvæ must hatch out, move down to the skin and break the surface of it in order to feed. The sheep maggot fly will lay its eggs on a fresh wound but it is also attracted by odours of decomposition. Thus a fleece contaminated with fæces, with blood, or with discharges from suppurating feet or even with decomposing bracken fronds, will be attractive to the fly. In Australia the chief attractant is furnished by the urine which soaks into the thick folds in the breech region of Merino sheep. Moreover, under certain climatic conditions the skin debris at the base of the wool fibre may undergo bacterial decomposition and the odour from this is often a very powerful attractant so that fly-blow occurs on apparently clean wool.

Once the fly has laid its eggs the successful hatching and development of the larvæ depend upon the microclimate in the sheep's fleece and it is only under suitable conditions of humidity and temperature that the fly-blow develops into a strike. If conditions are suitable the larvæ hatch and make their way down to the skin. Here they scratch the surface of the skin with their powerful mouth hooks and produce an inflammatory reaction which soon develops into a raw open sore on the exudations from which the larvæ feed. They also pour out a large quantity of slimy saliva which has a macerating effect on the underlying tissue. The successfully established strike produces ideal conditions for the attraction of more flies, the laying of more eggs, and the development of more larvæ and, if conditions are favourable to the larvæ, the wretched sheep may be literally eaten alive.

The types of disease with which we have dealt so far are those produced by the ectoparasites causing damage to the skin and the mechanism of disease production is fairly well understood.

Quite a different type of disease is the paralysis produced by certain ticks. Typically it is a rapidly ascending motor paralysis which sets in four to five days after the offending tick has attached. Paralysis first affects the limbs and later the head and neck. Respiratory distress may occur, and death, if it occurs, is usually due to respiratory failure.

Cases of this disease have occurred in both humans and animals in U.S.A. and in British Columbia following attachment of *Dermacentor andersoni* and in Australia following the bite of *Ixodes holocyclus*. Tick paralysis has also been noted in sheep in South Africa attacked by *Ixodes pilosus* [5]. For example, there is on record in America an outbreak of tick paralysis in cattle heavily infested with *Dermacentor andersoni*. 22 out of 186 yearling beef steers were affected with varying degrees of paralysis and many others showed symptoms of slight inco-ordination. Three beasts died, but all the remainder recovered when the animals were moved on to tick-free pastures and the ticks removed from them [6]. This is a characteristic of the disease and, in both human and animal cases, if the offending ticks are removed before the case has gone too far, then complete recovery follows. It seems certain that tick paralysis is due to the injection of a toxin secreted by the salivary glands of the tick and in the case of *Ixodes holocyclus* in Australia it has been found possible to reproduce the symptoms of dog-tick paralysis in mice by the injection of tick salivary gland [7].

Gregson, in British Columbia [8], states that paralysis in that area is produced only by fast-feeding ticks which engorge and detach after seven to eight days. By histological examination of biopsy specimens he showed that with fast-feeding ticks there were acute inflammatory changes in the derma but there was very little change at the site of attachment of slow-feeding ticks. He suggested that the tick is dependent for its access to blood fluid upon the production of œdema and hæmorrhage. The marked inflammatory changes produced by the fast-feeding ticks were, he thought, possibly due to the production and injection of a powerful toxin and he implied that this toxin might also produce the general result of paralysis.

This piece of work has not, so far as I know, been confirmed. In fact, the information on the exact mechanism of tick feeding is rather scanty and there seems room here for a good deal of work—not only in relation to tick paralysis but also to the multitude of tick-borne diseases. Our knowledge of the mechanism of transmission might be materially increased if we had more records of careful histological examination of the actual points of attachment of the various tick species.

Tick pyæmia.—Before I turn to the various diseases transmitted by ectoparasitic vectors I should like to mention an intermediate type of disease in which the infecting organism

may enter through the wound made by the parasite, which does not act as a true vector. It seems now fairly certain that tick pyæmia of lambs is brought about in this way. This is a disease which affects only young lambs on tick-infested pastures in this country and it is a pyæmia caused by a staphylococcus. Its constant association with tick infestation suggested that the tick might be the vector but Foggie [9] has shown that this is unlikely.

Staphylococci, similar to those isolated from the abscesses in affected lambs, were detected in the natural orifices and on the skins of ewes and on the skins of lambs. The exact mechanism by which this disease is produced has yet to be worked out. It seems certain that the tick has some association with it but it does not play the role of a true vector.

Ectoparasites which Act as Vectors

We now come to the vast field of disease production by ectoparasites acting as vectors of various pathogenic organisms. I can make but a brief reference to the many diseases and the factors involved in their production.

We have, first of all, the accidental carriage of infection by parasites which visit a number of hosts in rapid succession or contaminate their foodstuffs with pathogenic organisms. There is nothing mysterious about the mechanism of mechanical transfer of infection. Thus contagious ophthalmia of cattle is caused by a Rickettsia which can be mechanically transferred by flies like *Stomoxys calcitrans* and *Musca domestica* [10]. Anaplasmosis of cattle can be transmitted by Tabanids which are probably of importance in spreading the infection within the herd [11]. Tabanids are also of importance in the mechanical transmission of trypanosomes and there is evidence that these biting flies are of considerable importance during epidemics of sleeping sickness. Finally, it has been experimentally shown that bovine mastitis can be transmitted from cow to cow by flies feeding on infected secretion and then visiting the healthy udder [12].

The various ways in which disease pathogens are carried by vectors have been classified by Huff [13] who distinguished four types:

(i) In which the pathogen goes through a cycle of changes in the vector and also multiplies. There are various examples of this type, e.g. the malaria plasmodia carried by mosquitoes, the piroplasms and Theileriæ in ticks, and the trypanosomes in the tsetse fly.

(ii) In which the pathogen goes through a cycle of development in the vector but does not multiply—as in the case of the microfilariæ transmitted by mosquitoes.

(iii) In which the pathogen undergoes no cyclical change in the vector but multiplies inside it. Examples of this type are the multiplication of *Rickettsia prowazeki* in the louse and the multiplication of the plague bacillus in the foregut of the rat flea.

(iv) Finally he recognizes the purely mechanical transmission in which there is neither cyclical change nor multiplication. We have already considered examples of this type.

The different methods by which the disease pathogens enter the vertebrate host—that is to say the actual mechanisms of infection—are of great interest.

First of all there is the method of simple inoculation during the act of feeding of the blood-sucking vector. For this it is necessary that the pathogen should be present in the salivary glands of the vector and be injected into the wound with the salivary secretion. There are some interesting variations here.

The ticks which transmit East Coast fever of cattle—chiefly various species of Rhipicephalus—do not transmit the infection during the first two days of feeding but only after the third day [14] and it has been shown [15] that it is the act of feeding by the tick which induces the development of the infective stages (sporozoites) from the sporoblasts in the cells of the salivary glands, so that they are ready to pass out into the wound between the third and fifth days after attachment of the tick. Having fed, the East Coast fever tick empties itself completely of infection and in the next stage is no longer infective. This means that the tick cleans itself if it feeds on a non-susceptible animal. In this there is a marked contrast with the behaviour of the piroplasms which cause redwater in cattle for they, on the other hand, may persist through several generations of ticks which have fed on non-susceptible hosts [16]. The Babesia parasites are always passed through the egg to the next generation of tick and the infected tick does not clean itself in the act of feeding.

There are, of course, many diseases which are transmitted by direct inoculation of the pathogen in the saliva of the vector but there are several other ways in which transmission can occur. For example, plague bacilli may be transmitted by the rat flea *Xenopsylla cheopis* during the act of sucking but it has been considered that this transmission is the result of

temporary blocking of the entrance to the stomach with resulting regurgitation of contaminated blood into the wound [17].

A common method of transmission is by the infection through abraded skin or through mucous membrane contaminated with the infected fæces of the vector. This is the chief method of transmission of the Rickettsia of louse-borne typhus. Whenever a louse bites it makes a small puncture in the skin and defæcates at the same time. Since the louse bite is irritating, the bitten person usually scratches and may rub the louse fæces into the injured skin. The same method of infection is used by the trypanosome of Chagas' disease which is carried by a reduviid bug. The fæces of the bug are highly infective and invasion occurs as a result of scratching.

Finally, some diseases can be produced by the ingestion by the host of the infected parasite which may be crushed between the teeth.

The factors which enter into the production of disease by an arthropod vector are very complex indeed. Some disease pathogens are host-specific, like the piroplasms which produce redwater and biliary fever in domestic animals, but this host-specificity may extend only to the vertebrate host—there may be several vectors. Since the piroplasms are host-specific one can understand how necessary it is for them to persist in both the host and the vector and we find the piroplasms are transmitted through the egg and persist through several generations of the tick, and recovered animals remain carriers for very long periods. Again, we contrast East Coast fever. Animals recovered from this disease have a permanent sterile immunity and the pathogen easily dies out in the tick so that unless there was some reservoir for the Theileria it is difficult to see how it could survive. Little is known about the reservoir of infection for this disease, but there is some evidence that wild fauna and, in particular, eland and buffalo, provide the reservoir [18].

Many disease pathogens, and particularly the virus and rickettsial infections, have a very wide range of hosts and also of vectors, and a knowledge of the reservoirs of infection is very important. With some of the virus diseases the reservoir is all important and the appearance of the diseases in man or in domestic animals may be accidental. For example, the virus of western equine encephalitis is probably kept going in nature by small mammals and birds and carried by mosquitoes—and infection in man and horses is relatively infrequent.

The population density of the arthropod vector and the chances of contact with a susceptible host are both important factors concerned in disease production by ectoparasites. Thus, for example, sheep which have never been exposed to tick infestation and which have no degree of immunity against tick-borne fever fall a ready prey to this disease if they are introduced on to ticky pastures, even though the numbers of ticks are very small.

An interesting example of a high incidence of disease associated with a low incidence of the vector is quoted by Nash [19] who describes conditions at a small African village in which 70% of the 43 inhabitants were infected with sleeping sickness trypanosomes. He traced the infection to a small spot in a stream-bed where villagers came each day to fill their waterpots. Each woman had to spend about fifteen minutes to fill her waterpots so that for many hours a day a very small tsetse population could feed on a queue of women without expending much energy in search of food.

In most cases the arthropods which act as vectors of the viruses and Rickettsiæ are infected by them and remain infected as long as they live and, in some cases (e.g. in louse-borne typhus), a heavy infection may even result in the death of the vector. Infection of Rhipicephalus ticks with *Theileria parva* on the other hand is not permanent and the infection dies out within twelve months of moulting if the tick has not fed. Moreover, if the infected larval or nymphal tick is exposed to a temperature of 35°C.–38°C. during the moult the infection never develops [18].

The ability of the organism to infect various organs in the vector determines, to some extent, the mode by which its transmission and survival will be effected. If the salivary gland becomes infected then direct transmission by blood sucking may follow. If the organisms multiply in the gut but do not infect the salivary gland, then we should expect transmission to be by way of the fæces of the vector or by actual ingestion of the body of the vector. If the ovary of the vector is infected, we should expect survival of the organism through the egg to the next generation of the vector.

What I have said in opening this discussion does not do justice to the complexity of the subject but it does emphasize the very great importance of ectoparasites in the production of disease in man and animals. Our knowledge of all the factors involved is far from

complete but a great wealth of knowledge exists which is serving as a basis for many successful schemes of disease eradication. The advent of modern insecticides renders it more possible to control these diseases by attacking the vectors which carry them. We have already seen the success of control of the Naples typhus epidemic and the elimination of malaria from Cyprus, and many other examples, but none of these successes or of those which may come in the future will have been possible without a thorough knowledge of the vectors and of the mechanisms by which they produce disease in their hosts.

Sometimes some of the knowledge gained in the study of these mechanisms may seem academic but, in the end, all of it is valuable in piecing together the story and enabling us to understand the epidemiology of the disease and, eventually, to arrive at satisfactory methods of control. And this, surely, is our ultimate aim.

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Mr. A. W. McKenny Hughes: I have had some experience of the ecology of the bed-bug (*Cimex lectularius*), and whilst the bed-bug is not, so far, incriminated as a disease carrier, it can and does produce deleterious effects in children and certain adults. When working in this field, I could pick out children coming from "buggy" homes by their pasty faces and listless appearance, even when separated from their environment. This condition was not due to the unhygienic standards which usually accompany bed-bug infestation, nor the loss of blood from the bites, but to the injection of the bugs' saliva, the consequent irritation, and loss of sleep. A great deal of distress and sometimes quite high temperatures can be caused by the bites of insects of various species. Sometimes only a mass attack will produce this result, at others one bite only may be necessary.

The bed-bug and the louse (*Pediculus humanus*) have two different types of bite. The bed-bug carries a proboscis or beak outside and under its head when it is not feeding, the end tucked away between the front coxæ. When it wants to feed the rostrum is brought forwards and downwards and the bug then proceeds to find the exact spot it prefers. It may be quite particular about this and discard several likely sites before it is satisfied, it may even draw a little blood from some of them. When satisfied that it has found the ideal place it thrusts the proboscis, which is only a grooved outer sheath protecting the stylets, downwards and usually slightly forwards. The proboscis corresponds with the labium. When this comes in contact with the skin it buckles and allows the stylets to be thrust in. There are two pairs: the outer, corresponding to the mandibles, are saws, and the inner pair (maxillæ) are knives. Together they form two tubes, small for the saliva and a larger one to suck up the mixture of saliva and blood. There is a pharyngeal pump in the head which, by expanding and contracting muscles, opens and closes the pharynx and pushes the mixture back to the stomach. If the bug were proved to carry disease it would have to do so in the act of biting as it seldom, if ever, defæcates on the host.

The louse on the other hand has a much more complicated biting mechanism. All the mouth-parts are carried inside the head except when the insect feeds. In front of the head is a short, soft tube called the haustellum with teeth attached, possibly the labium. When the louse wants to feed it pushes this tube more or less inside out so that the teeth are now outside, the insect uses these rather like drawing pins to keep the mouth parts in place when feeding. Behind are the buccal cavity more or less rigid, a cibarial pump, a pharynx divided by constrictions and each able to move independently by muscles. The pharynx leads straight into the œsophagus which is narrow and not muscular. In a lower blind cavity are the three stylets, dorsal, ventral and intermediate, but dorsal and ventral stylets are toothed, the middle stylet is a free tube carrying the saliva. In feeding the stout ventral stylet probably pierces the skin, the dorsal stylet folds up to form a food canal. In short then, what appears to happen is that the mouth-parts are tethered by the teeth, the stylets excoriate the skin rather as in vaccination, the saliva is passed to the wound and the "mixture as before" digested. There is one slight similarity, however, that the proboscis of the bed-bug and the haustellum of the louse both act as a tubular guide for the stylets.

The louse transmits *Rickettsia prowazeki* from one human being to another and exanthematous typhus is the result. The Rickettsias develop inside the lumen and epithelial cells of the midgut and after a few days appear in enormous numbers in the creature's fæces. As the louse, unlike the bed-bug, relieves itself at all times especially when feeding, the transmission of typhus is thought to be almost entirely through the scratching or crushing of the fæcal pellets into the wounds made by the insect bites. It is possible that some infection may be caused by squashing the lice themselves. One final way that typhus may be contracted is airborne, fæces getting into the conjunctiva of the eye or into the respiratory tract; for instance, blankets shaken in the wind releasing large numbers of louse fæces.

Looked at the other way round the louse can pick up Rickettsias either in feeding or in swallowing infected fæces on the surface of the skin. The louse is also responsible for trench fever. It is very odd that this disease appeared on the Western Front in the 1914–18 war and then died out completely, and so far as is known has not been seen since. There is some confusion in Ethiopia about a fever very like trench fever in laboratory workers making anti-typhus material, though *R. quintana* was not isolated in this outbreak.

The louse can carry the spirochæte of relapsing fever, *Spirochæta recurrentis*. There is a tick-borne relapsing fever and a louse-borne; neither creature can carry the other's spirochæte. In the louse the spirochætes are picked up in feeding and are found in the human blood in the louse's midgut up to a day after an infected meal. After this they disappear. After some six days—some people say a few hours—the spirochætes appear in the louse's blood in the hæmocœle, from which there is no way out, unless the louse is damaged. It is thought that this is, in fact, what does happen. They get squashed or damaged by the host and thus release spirochæte-infected blood into the skin. It has always seemed to be a weak argument that the spirochætes found their way out of the louse's gut into the hæmocœle, but could not get back again. Nevertheless this may be all part of the complicated development, since the disease cannot be transmitted from man to man except through an intermediate host.

The common housefly *Musca domestica*, a deadly creature with revolting habits, transmits disease in a totally different way. It can pick up and transmit the organisms of typhoid, cholera, dysentery, diarrhœa—especially summer diarrhœa in children—and certain eye, worm, and skin diseases. There are various ways in which the fly does this. The fly can and does alternate between fæces and your food in quick succession. The fly has a bilobed proboscis under the head which is retractable. In feeding the fly puddles its food with this process, vomiting up the contents of the front gut to liquefy the food under immediate consideration; when this has been done it sucks back the resulting mess. The implications of this are obvious. The vast majority of fly-borne excremental disease is transmitted in this way. It can, however, convey pathogenic organisms in its fæces which are passed anywhere or on its feet, legs, body or wings, i.e. mechanically.

Dr. R. E. Rewell: The mysterious effects of the bed-bug on man may be contrasted with his lice, although these are far more frequent and numerous. Such phenomena may sometimes be due to the carriage of unrecognized pathogens. Thus at the Zoological Gardens we know that infestation with *Ophionyssus serpentium* is often fatal to snakes, while recent work in the U.S.A. has shown these to be vectors of the deadly *Proteus hydrophilus* which we had overlooked.

Sarcoptes scabei may attack many different hosts, but its burrows may be of different extent, and at a different angle to the surface, in each. It is transmissible from man to the gorilla

and orang-utan, but probably not to the chimpanzee. There seems to be no explanation for such discrimination.

Dr. E. G. White referred to the very varied susceptibility of human beings to insect bites and suggested that hypersensitivity, rather than immunity, was the important factor. The very violent local reactions of some persons to insect bites seem to persist in spite of very frequent attacks: desensitization did not seem to occur in such cases. It would be of interest to know the reaction of very young children to insect bites, as compared with their reactions in later life. Did those adults who showed little reaction possess this feature from birth or did they at one time react violently? Were violent reactions constant in certain persons throughout their life or did they change as a result of repeated exposure? It seemed that we knew very little of the behaviour of man and animals to insect bites and still less of the mechanisms involved.

Section of Experimental Medicine and Therapeutics

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RECENT WORK ON VITAMIN B_{12}

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Isolation and Chemistry of Vitamin B_{12}

In 1946, that is to say twenty years after the initial discovery by Minot and Murphy of the efficacy of liver in pernicious anæmia, my colleagues Emery and Parker (1946) announced the preparation of a concentrate fully effective in a single dose of 1 mg. This achievement seemed so remarkable at the time that the claim was received with some scepticism. Yet in another two years we had the preparation one hundred times more potent, viz. the crystalline anti-pernicious factor itself, now generally known as vitamin B_{12}.

The secrets of this greatly accelerated progress were, first: the use of new fractionation techniques, especially chromatography and, secondly, improved assay facilities. The U.S. team invented a new microbiological assay method, while we were fortunate in enlisting the assistance of Dr. C. C. Ungley with a large number of suitable clinical cases. The American team, directed by Dr. Karl Folkers of Merck & Co. Inc., have published some of the chemical and physical properties of vitamin B_{12} isolated both from liver and from *Streptomyces griseus* fermentation liquors (Rickes, Brink, Koniuszy, Wood and Folkers, 1948*a*, 1948*b*; Brink, Wolf, Kaczka, Rickes, Koniuszy, Wood and Folkers, 1949). They have, however, released no details of methods of isolation except in a recently published patent specification which indicates that, like ourselves, they found chromatography to be the key to the problem. The isolation of crystalline vitamin B_{12} in Glaxo Laboratories was announced only a few weeks later, and was later followed by information about our isolation techniques (Lester Smith, 1948; Lester Smith and Parker, 1948; Fantes, Page, Parker and Lester Smith, 1949). In our hands the relatively new technique of partition chromatography, invented by Martin and Synge (1941), proved invaluable. Our product was later shown to be identical with that isolated by the Merck workers; vitamin B_{12} has since been isolated in other industrial laboratories in Britain, America and Holland.

Beginning with a commercial liver extract we usually applied at least six chromatographic procedures in succession, interspersed with other steps of purification, such as salting out with ammonium sulphate, proteolysis, precipitation with phosphotungstic acid and partition between aqueous solutions and solvent mixtures. The chromatographic steps included adsorption on alumina, silica and charcoal, elution being effected usually with aqueous alcohol, as well as partition chromatography on moist silica using butanol as flowing solvent. Some of these steps had to be repeated. This complicated succession of steps was necessitated by the approximately millionfold concentration involved in passing from liver to pure vitamin B_{12}. Unfortunately, the substance had no chemical properties that could be usefully employed to separate it from impurities. We had therefore to rely almost entirely on physical methods. Naturally the losses *en route* were considerable and we considered ourselves fortunate to finish with 20 mg. from a ton of liver. We have been able to obtain larger amounts, though with not very much less difficulty, from *S. griseus* fermentation liquors.

Vitamin B_{12} occurs as dark red needles. The anhydrous substance has a molecular weight of about 1,300. It is remarkable in containing not only the usual elements, carbon, hydrogen, oxygen and nitrogen but also phosphorus and, most surprising of all, cobalt. It has a rather characteristic absorption spectrum, the main bands being one in the ultraviolet at 360 mμ and one in the visible at 550 mμ. A large number of its physical constants have been determined but they have not so far been of much value in helping to elucidate the structure of this somewhat complex molecule. Vitamin B_{12} appears to be stable in the solid state and also in solution at neutral or slightly acid pH values. It is not completely destroyed, for example, during several days at room temperature at extreme pH values of 2 or 12. Hydrolysis by boiling with strong acid, however, disrupts the molecule, liberating the following substances: phosphoric acid, ammonia, dimethylbenzimidazole, an unidentified compound giving a weak ninhydrin reaction and a red cobalt-containing acidic substance, which still comprises the greater part of the original molecule (Ellis, Petrow and Snook, 1949; Beaven, Holiday, Johnson, Ellis, Mamalis, Petrow and Sturgeon, 1949; Cooley, Ellis and Petrow, 1950). Little more is known except that on fusion with alkali it yields pyrrole-like substances. Its physiological mode of action is equally a mystery. We had hoped to determine at any rate its site of action by using vitamin B_{12} labelled with radio-active cobalt or phosphorus but so far our attempts to prepare the vitamin "tagged" in these ways have not been successful.

There are three or more forms of vitamin B_{12}, all active both microbiologically and clinically. My colleagues and I were the first to produce chromatographic evidence for a second and possibly a third form. One of these, called vitamin B_{12b}, was, however, first obtained crystalline by a team at the Lederle Laboratories (Pierce, Page, Stokstad and Jukes, 1949). In the meantime vitamin B_{12a} had been prepared by catalytic hydrogenation of vitamin B_{12} by the Merck workers. It now appears to be identical with B_{12b} (Kaczka, Wolf and Folkers, 1949; Brockman, Pierce, Stokstad, Broquist and Jukes, 1950). My colleagues and I at Glaxo Laboratories have lately isolated another crystalline factor, for which the name vitamin B_{12c} is now proposed (Buchanan, Johnson, Mills and Todd, 1950).[1] Its clinical activity will be mentioned in succeeding papers.

This, however, does not end the complications; evidence is accumulating for various forms of bound vitamin B_{12}, probably linked with peptides or proteins. Such bound forms appear to occur, for example, in liver, in fermentation liquors and possibly in milk. Ternberg and Eakin (1949) have shown that vitamin B_{12} appears to combine with a constituent of gastric juice, presumably Castle's intrinsic factor, to produce a non-dialysable microbiologically inactive complex. On autoclaving, however, free vitamin B_{12} is released again. Further, although it appears certain that vitamin B_{12} will do anything, clinically speaking, that a liver extract can do, it is perhaps premature to dismiss entirely the earlier "multiple factor theory" put forward by Jacobsen and others. In other words it is still possible that other factors may exert a "sparing action" on vitamin B_{12}. Certainly evidence is beginning to accumulate that folic acid as well as vitamin B_{12} may be needed for the control of some anæmias. It is now well established that vitamin B_{12} is needed by chicks, turkeys and pigs on diets low in animal protein. In this field again there is some evidence that one or more of some additional unidentified factors may be essential for optimal growth.

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[1] At the meeting vitamin B_{12c} was referred to as "the unnamed factor" or as "vitamin B_{12X}"—a temporary designation.

C. C. Ungley, M.D., F.R.C.P., *Physician, Royal Victoria Infirmary, Newcastle upon Tyne*:

Vitamin B_{12} and other Dietary Factors in Megaloblastic Anæmias and in Subacute Combined Degeneration of the Cord

Two groups of megaloblastic anæmia will be considered: pernicious anæmia, in which gastric atrophy leads to permanent loss of Castle's intrinsic factor and deficient absorption of vitamin B_{12}; and non-Addisonian megaloblastic anæmias associated with pregnancy and intestinal disorders where a different mechanism is at work.

The effects of parenteral administration of vitamin B_{12} in pernicious anæmia have already been described (Ungley, 1949*b*). Single doses of 10 μg. or more produced, on average, a maximal reticulocyte response. A better yardstick, however, is the increase of red blood cells in fifteen days. Ten μg. produced a response up to the "average" standard of Della Vida and Dyke (1942), but doubling the dose anywhere in the range from 5 to 80 or even 160 μg. produced a constant increase in response. It was thus possible to forecast the expected response to any dose within this range. The response in single cases might deviate from the expected response by 300,000 cells per c.mm. but for groups of 10 cases the error was not usually more than 100,000 cells.

About 80% of the total increase of red blood cells in 15 days occurred in the first ten days (Ungley, 1949*b*).

These findings form a useful basis for comparison, for example, in assessing the efficacy of vitamin B_{12} in other types of megaloblastic anæmia and for comparing vitamin B_{12} from liver with a similar red crystalline compound obtained from *Streptomyces griseus*.

Vitamin B_{12} in subacute combined degeneration of the cord.—Maintenance doses of 10 μg. a fortnight have prevented the development or exacerbation of neurological disorders in pernicious anæmia although larger doses are desirable for routine use.

More direct evidence of the efficacy of vitamin B_{12} against the neurological manifestations of pernicious anæmia has been obtained by the intensive treatment of 9 fully-established cases of subacute combined degeneration of the cord (Ungley, 1949*c*). Neurological findings were assessed on a quantitative basis and scored. During a control period anæmia was counteracted in some cases by transfusion without improvement in the neurological condition. Subsequently the weekly injection of 40 microgrammes of vitamin B_{12} led to a gradual reduction in the total score for neurological defect. Improvement continued for about six months leaving, as usual, a residuum of irreversible damage in the nervous system. The degree of improvement was related to the duration of the disease as measured by the duration of difficulty in walking. Comparison with 44 cases treated before the war showed that vitamin B_{12} was as effective as parenteral liver extracts, whether crude or refined.

Cobalt-containing red pigments related to vitamin B_{12}.—(1) *Free forms*: Vitamin B_{12a} is an artificial product obtained chemically by hydrogenation of vitamin B_{12}.

Vitamin B_{12b} is a constituent of liver extract and appears in the slow-moving red component of the chromatogram.

An allied substance, now named vitamin B_{12c}, has been isolated by Lester Smith from *Streptomyces griseus*.

All these factors are clinically active when administered by injection.

Comparisons between crystalline vitamin B_{12c} from *Streptomyces griseus* and vitamin B_{12} from liver have been made firstly on the basis of the increase of red blood cells in fifteen days following a single dose. 17 patients with pernicious anæmia in relapse have received single doses of 10, 20, 40 and 80 μg. On the average, the responses are equal to those which would be expected from similar doses of vitamin B_{12} obtained from liver.

Secondly, improvement has been observed in 3 patients with subacute combined degeneration of the cord, but it is too early to say whether there is any quantitative difference between the effect of this substance and that of crystalline vitamin B_{12} obtained from liver.

Thirdly, requirements for maintenance are being assessed.

Fourthly, comparisons are being made by the double reticulocyte response method.

(2) *Bound forms*: "Animal protein factor" is apparently the same as vitamin B_{12} either free or bound. Information about bound forms of vitamin B_{12} is scanty. They are probably unavailable to bacteria and inactive by injection. When given by mouth the linkage to protein is presumably split by gastric or pancreatic digestion.

Interrelationship between vitamin B_{12} and folic acid and other nutrients.—In bacteria needs for vitamin B_{12} can be partly met by thymidine and certain other deoxy-ribosides, or even under some conditions by ascorbic acid or methionine.

In a case of pernicious anæmia the injection of 48 mg. of thymidine produced a negligible response (Ungley, 1949*a*). Hausmann (1949) claims positive results with doses of 1 to 2 grammes. This is approaching the enormous doses required for thymine.

We know little about the interrelationship between folic acid and vitamin B_{12}, but three questions may be considered.

Firstly, do patients with pernicious anæmia ever need folic acid in addition to vitamin B_{12}?

Patients with pernicious anæmia with or without subacute combined degeneration of the cord can be successfully treated for indefinite periods with refined liver extracts or vitamin B_{12}. The following is an exceptional case in which vitamin B_{12} failed until needs for folic acid had been met. The patient was a man aged 55 years. Treatment for syphilis had been successfully completed some months before, otherwise the case was typical of pernicious anæmia with complete achlorhydria and megaloblastic marrow. His diet had been reasonably good. The first dose of 10 μg. of vitamin B_{12} produced a very poor response. Thereafter small amounts of folic acid, 15 mg. in all, led to a satisfactory reticulocyte response and increase in red blood cells. When the hæmatopoietic effects had worn off and counts were falling a similar dose of the same batch of vitamin B_{12} caused a satisfactory increase in red blood cells. This case recalls the pigs described by Heinle, Welch and Pritchard (1948) which were so completely depleted of hæmatopoietic factors that folic acid failed unless liver extract was supplied; and liver extract failed unless small amounts of folic acid were supplied.

I should like to stress here once again, that this case is exceptional and that ordinary patients with pernicious anæmia and subacute combined degeneration can be treated for years without requiring the administration of anything more than refined liver extract or vitamin B_{12}. Does this mean that vitamin B_{12} aids in the synthesis of folic acid in man as it seems to do in chicks (Dietrich, Nichol, Monson and Elvehjem, 1949), or that there was no deficiency of folic acid in the first place?

Patients with pernicious anæmia are said to have difficulty in deriving free folic acid from conjugated forms in natural foodstuffs, many of which contain conjugase inhibitors. Even some of the responses to pure folic acid conjugates (pteroyltri- and di-glutamic acids (Wilkinson and Israëls, 1949)) were not very good considering the large doses administered.

Nevertheless patients with pernicious anæmia seem able to excrete in the urine as large a percentage of a loading dose of 20 mg. of folic acid as do normal persons. This does not suggest any deficiency of folic acid but tests must be repeated using smaller—"more physiological"—loading doses.

The second question is, why do some patients with pernicious anæmia treated with folic acid alone respond first but later become progressively worse even if the dose is increased? Why should folic acid work at all if there is no deficiency of this substance? Is it that an excess of folic acid improves the function of traces of vitamin B_{12} still remaining in the tissues? On this hypothesis the increased tendency to involvement of the nervous system would be explained by an accelerated utilization and ultimate exhaustion of these traces of vitamin B_{12}.

Even in megaloblastic anæmia associated with the sprue syndrome prolonged administration of folic acid alone may lead to neurological disorders. This occurred in 2 patients described by Davidson and Girdwood (1948), and in one of my own who developed a psychosis which responded promptly to a source of vitamin B_{12}.

The third question is, can folic acid potentiate the action of small doses of vitamin B_{12}? In a patient with pernicious anæmia the daily injection of 0·5 μg. of vitamin B_{12} led to a reticulocytosis. Thereafter the same daily dose of vitamin B_{12} supplemented by 100 μg. of folic acid caused a second reticulocyte response. This, however, may have been merely a summation of effects and not a catalytic effect. In another patient the dose of vitamin B_{12} in the second period was reduced to 0·4 μg. and there was no secondary reticulocytosis. Much more work is necessary before conclusions can be drawn.

In chickens, feeding folic acid increased the stores of vitamin B_{12} in the liver and giving vitamin B_{12} increased the stores of folic acid (Dietrich, Nichol, Monson and Elvehjem, 1949). We do not yet know whether the same is true in man.

Absorption of vitamin B_{12} from the alimentary tract.—When vitamin B_{12c} from *Streptomyces griseus* and later vitamin B_{12} itself were given by mouth in the enormous dosage of 80 μg. a day the responses were poor. After a total of 1,920 μg. in twenty-four days the increase of red blood cells was less than half the expected increase in fifteen days from a single injection of 5 μg: it was in fact rather less than the mean increase in fifteen days observed in 6 patients who received a single injection of 2·5 μg. (Ungley, 1949*b*, Table V). The subsequent daily administration of only 1 μg. by injection was followed by a satisfactory rise of red blood cells (equivalent to the expected rise from a single dose of 10 μg.). In this case the amount of orally administered material necessary to produce a given response was several hundred times that which would have been required by injection.

The daily administration of 5 μg. of vitamin B_{12} by mouth was ineffective whereas the same quantity given daily with 50 ml. of normal unfiltered gastric juice produced a satisfactory response. A total of 75 μg. in fifteen days produced an increase of erythrocytes equivalent to the response expected from a single dose of 10 μg. by injection.

In another case similar amounts of material for ten days produced a response equivalent to that expected from 20 μg. by injection.

Incidentally filtration of the gastric juice through a Seitz filter led to loss of most of the intrinsic factor activity.

In one case the administration of 40 μg. of vitamin B_{12} given with only 150 ml. of gastric juice as a single dose was inadequate.

In another patient a single dose of 50 μg. and 500 ml. of gastric juice given by stomach tube produced a good response. The increase in red blood cells in fifteen days more than equalled the expected response from a single dose of 40 μg. by injection.

Further work is necessary but in the 3 cases mentioned the amounts of vitamin B_{12} which had to be given orally with gastric juice were approximately 1·25, 2·5 and 8 times as great as would have had to be given by injection to produce the same effect (*see* Ungley, 1949*b*). Possibly the results might be more consistent with larger amounts of gastric juice.

Does intrinsic factor directly facilitate the absorption of vitamin B_{12} or merely prevent its destruction in the gastro-intestinal tract?

The daily application of 5 μg. of vitamin B_{12} to the mucous membrane of the floor of the mouth produced no hæmatopoietic response, whereas the same quantity given by mouth with 50 ml. of gastric juice produced a good response, equivalent to the response expected from a single injection of 20 μg.

We next tried to determine whether vitamin B_{12} would be absorbed from the intestine without gastric juice if we prevented contact with intestinal contents which might destroy it or render it unavailable.

A segment of small intestine was isolated between two balloons on a Miller-Abbott tube. This segment was washed clear of intestinal contents and 40 μg. of vitamin B_{12} was instilled. A small sample withdrawn after one hour still showed a high vitamin B_{12} content. There was no hæmatopoietic response. Later the same amount of vitamin B_{12} given orally with 150 ml. of normal gastric juice produced a reticulocyte response. The response was submaximal probably because the volume of gastric juice was too small. An increase of erythrocytes almost equal to the predicted response followed the injection of 40 μg.

Contents aspirated from various levels of the small intestine have been assayed microbiologically by Dr. W. F. J. Cuthbertson. The subjects were 2 untreated cases of pernicious anæmia. Some samples contained thymidine or minute amounts of vitamin B_{12}. No greater amounts were released after heat or digestion with papain. The intestinal contents did not contain anything which inhibited the growth of the lactobacilli.

The remarkably high excretion of vitamin B_{12} in the stools of patients with pernicious anæmia reported by Callender, Mallet, Spray and Shaw (1949) is not necessarily due to deficient absorption—it might equally well be due to biosynthesis of vitamin B_{12} in the colon.

Is there any interaction of vitamin B_{12} and intrinsic factor?

In microbiological assays carried out last year Cuthbertson and I were surprised to find that what little vitamin B_{12} activity there was in a beef digest disappeared after incubation with normal gastric juice, whereas pernicious anæmia gastric juice had little or no effect.

Recent work by Ternberg and Eakin (1949) seems to show that something in the gastric juice (probably Castle's intrinsic factor) combines with vitamin B_{12} *in vitro* and renders it unavailable to bacteria. The combination seems to be quite loose. Heating the compound breaks the linkage and leaves the vitamin B_{12} once again available to bacteria.

We still do not know whether this combination with a gastric factor facilitates absorption of the vitamin or merely protects it from destruction in the gastro-intestinal tract.

Vitamin B_{12} in megaloblastic anæmias of pregnancy.—In 6 cases of megaloblastic anæmia associated with pregnancy or the puerperium, the injection of vitamin B_{12} in doses of 65 to 80 μg. was completely ineffective except for a slight reticulocytosis in one case. The patients subsequently responded to folic acid, often in small doses—2·5 μg. daily (Ungley and Thompson, 1950).

Vitamin B_{12} in megaloblastic anæmias associated with intestinal disorders.—Here the results are variable.

In a case associated with intestinal stenosis the injection of 80 μg. produced quite a good response. But even allowing for an initial fall in the first three days the increase of red blood cells by the fifteenth day was equivalent only to the response expected from 20 μg. in Addisonian pernicious anæmia.

In a patient with idiopathic steatorrhœa the response to 80 μg. of vitamin B_{12} was about equal to the response expected from 5 μg. in Addisonian pernicious anæmia.

A patient with steatorrhœa associated with thyrotoxicosis failed to respond to vitamin B_{12} whereas folic acid was effective.

Two further cases associated with steatorrhœa are now under treatment. One showed no response to vitamin B_{12} but a good response to folic acid. The other is responding to vitamin B_{12}.

Toxic and hæmolytic aspects.—Not all the facts can be explained on a simple nutritional basis. Both in true pernicious anæmia and in non-Addisonian megaloblastic anæmias toxic and hæmolytic factors may play a part. Since methæmalbumin may be present in the plasma some of the hæmolysis must be intravascular. Destruction of poorly formed red cells is not sufficient explanation. In collaboration with Dr. W. Walker we have followed the survival of transfused cells from normal donors. In most patients with pernicious anæmia such cells are eliminated at a normal rate, surviving about 120 days. In three cases, however, the transfused cells were rapidly destroyed. A change to a normal rate of elimination occurred after vitamin B_{12} in 2 cases and spontaneously in 1 case. In three patients with non-Addisonian megaloblastic anæmia associated with pregnancy or intestinal disorders excessive hæmolysis changed to a normal rate of elimination about two weeks after giving folic acid. The dramatic change in the rate of destruction after treatment suggests that vitamin B_{12} and folic acid may be concerned in detoxicating or preventing the production of a hæmolytic agent.

My colleague, Dr. R. B. Thompson (1950), confirms the finding of Rusznyák, Löwinger and Lajtha (1947) that the maturation of megaloblasts in marrow culture is accelerated by the addition of normal plasma but inhibited by "pernicious anæmia" plasma. The greater the concentration of "pernicious anæmia" plasma the less the megaloblasts mature. This suggests active inhibition rather than mere absence of a maturation factor. Low concentrations of folic acid (1 μg. / ml.) added to an inert medium caused rapid maturation of megaloblasts, but "pernicious anæmia" plasma antagonizes this effect. The maturing effect of small amounts of normal plasma is also antagonized by the addition of "pernicious anæmia" plasma. Larger amounts of folic acid or of normal plasma overcome this antagonism. Cerebrospinal fluid from patients with pernicious anæmia has an effect similar to their plasma so that the inhibiting factor is probably ultrafiltrable.

The action of vitamin B_{12} on maturation of megaloblasts *in vivo* is presumably indirect, for unlike folic acid it fails to accelerate maturation *in vitro*.

Other relevant facts follow:

Early lesions in the spinal cord in pernicious anæmia are spotty in distribution and often related to vessels. They suggest the action of a substance destructive to myelin rather than a simple nutritional deficiency.

The urinary excretion of certain phenolic compounds is excessive in relapse and becomes normal after treatment with vitamin B_{12} (Abbott and James, 1950).

Liver slices from rats deficient in folic acid failed to metabolize tyrosine completely until folic acid was added (Rodney, Swendseid and Swanson, 1949). Intermediary products of tyrosine metabolism include phenolic substances.

Another potentially toxic substance is indol, a product of the metabolism of tryptophane. Indol fed to pigs on a diet deficient in vitamin B complex produces hæmolysis and macrocytic anæmia, a result not observed in normal pigs (Rhoads, Barker and Miller, 1938).

For the production of macrocytic anæmia following intestinal stenosis, loops or blind sacs, stagnation and bacterial infection of intestinal contents seem to be essential. In the rats of Watson, Cameron and Witts (1948) many weeks elapsed before the animals became suddenly ill and anæmic. My tentative interpretation is that a toxic and hæmolytic factor was produced in the infected contents of the blind sac. During the latent period detoxication occurred through enzymes using folic acid and possibly vitamin B_{12}, stores of which were gradually depleted in the process. When these stores were exhausted detoxication failed, resulting in sudden illness and anæmia. Folic acid restored the power of detoxication and relieved the anæmia.

Something of the same kind may occur in pernicious anæmia where bacteria flourish in the small intestine in a medium rendered abnormal by lack of gastric acid and enzymes.

A tentative hypothesis based on these findings, some of which require confirmation, is that in megaloblastic anæmias toxic as well as nutritional factors play a part. These are responsible for megaloblastic erythropoiesis, for some of the hæmolysis and possibly for the lesions in the spinal cord. Potentially toxic material, for example indol or a phenolic compound, arises either from bacterial action on protein metabolites in the small intestine or from a defect in intermediary metabolism of some substance such as tyrosine or tryptophane. Detoxication or a return to normal metabolism in which production of toxic material ceases occurs through the action of enzymes using folic acid and vitamin B_{12}.

Yeast.—Wills' factor: Is there a hæmatopoietic factor other than vitamin B_{12} or folic acid present in whole liver and in yeast? Why should yeast extracts which appear to contain no vitamin B_{12} when tested microbiologically or in animals be effective as a source of extrinsic factor? In pernicious anæmia yeast extracts such as marmite have to be given in large doses (e.g. marmite 120 grammes) to produce even a moderate effect. When given with a source of intrinsic factor even small doses (e.g. marmite 12 to 24 grammes) are effective.

In megaloblastic anæmias associated with pregnancy and sprue, yeast extracts are sometimes effective by mouth in relatively small doses. Yet a patient with non-tropical sprue failed to respond to doses by injection, one-tenth of those which were successful when given by mouth. If vitamin B_{12} had been the effective agent injections should have been effective in doses 60 to 100 times less than the oral dose.

Can the effect be due to folic acid or folic acid conjugates?

In a patient with megaloblastic anæmia of pregnancy the daily dose of yeast extract which produced a good reticulocyte response contained less than 40 μg. of folic acid tested both microbiologically and in animals for conjugates. Moreover, the daily excretion of folic acid in the urine during the period of administration of the yeast was extremely low, only 1 to 5 μg. per day. During the next period 2·5 mg. folic acid daily produced no secondary reticulocyte response such as one might have expected if the initial response to yeast had been due to traces of folic acid. The mean excretion of folic acid now rose to 700 μg. per day. It is true that conjugase inhibitors in yeast make it difficult to assay folic acid conjugates microbiologically, but this difficulty does not apply to rat assays which were used as a check in this instance. This leads me to think that there may be a Wills' factor after all, despite current tendencies to explain the hæmatopoietic effect of yeast in terms of folic acid conjugates.

In conclusion I thank my colleagues, notably Dr. R. B. Thompson who has been responsible for marrow cultures, Dr. W. Walker who followed the survival of transfused erythrocytes and Dr. L. W. Carstairs for intubation of the small intestine. I am grateful to the medical, nursing and lay staff of the hospital and medical school and to many general practitioners for their co-operation. Dr. E. Lester Smith supplied the whole of the vitamin B_{12} used in this investigation and Dr. W. F. J. Cuthbertson was responsible for microbiological assays. I wish to thank both these members of the Research and Development Division of Glaxo Laboratories for their co-operation and Glaxo Laboratories for a research grant made to King's College, University of Durham, which provided for the Research Fellowship now held by Dr. R. B. Thompson.

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Observations on the Relationship between the Red Cell and Reticulocyte Responses and Changes in the Bone-marrow of Patients Suffering from Pernicious Anæmia Treated with Injections of Liver Extracts or Vitamin B_{12}.

This work has been carried out on a series of patients suffering from uncomplicated Addisonian pernicious anæmia. We have been particularly interested in the changes which take place in the red cell and reticulocyte counts of patients treated with single injections of liver extract or with vitamin B_{12} and the correlation of these changes with alterations in the cellularity and morphology of the bone-marrow which take place at the same time.

Several well-known brands of liver extract have been employed, both of British and American origin, all of known B_{12} content as judged by microbiological assay[1]. We have also had available to us, by courtesy of Glaxo Laboratories, a B_{12} concentrate prepared from *Streptomyces griseus* cultures and, in addition, preparations of B_{12c} and of crystalline B_{12} derived from liver.

Although about 30 patients have been studied, the observations that are now recorded are based on an intensive study of a relatively small group of typical cases. It is thought, nevertheless, that these observations have a general application.

Methods.—Venous blood has been used throughout. We have taken great pains with the red cell counts and have counted a minimum of 2,000 cells in each count; under these circumstances our results are believed to be accurate within ± 5%, a range embracing ± twice the coefficient of variation. Translated into figures, this means ± 100,000 cells per c.mm. in a two million count or ± 50,000 cells in a count of 1 million per c.mm.

The *reticulocytes* have been counted in dry, uncounterstained films made from the deposit, suspended in plasma, obtained after staining for 15 min. at 37° C. and then centrifuging a weak suspension of red cells in 0·4% cresyl blue in saline. As with all counts concerned with a varying proportion of abnormal cells, it is difficult to generalize as to the errors involved in these reticulocyte counts; with 10% of reticulocytes, the error is thought to have been about ± 20% of this percentage; with higher proportions of reticulocytes, the error is likely to have been less, and with lower proportions correspondingly greater.

The *bone-marrow* has been studied in smears made from material aspirated by sternal puncture; and in most patients a series of observations has been made.

Results.—The first point to be considered is concerned with the length of time a bone-marrow will remain normoblastic in type following a single injection of liver extract or vitamin B_{12}, given to a case of pernicious anæmia. With doses of liver extracts or of B_{12} of sufficient potency to produce a so-called "average satisfactory" rise in the red cells according to the criteria of Della Vida and Dyke (1942), the marrow is likely to have reverted to a partial megaloblastic state several days before the end of the fifteen-day period. Usually quite well-marked megaloblastic change is present by the eleventh day, and there may be early indications by the eighth day. This tendency to reversion after single injections are given is reflected in a falling off in the response in the peripheral blood. With smaller dosages the marrow may never become normoblastic at all, although "intermediate" types of megaloblasts may appear (*see* Dacie and White, 1949). In these cases, nevertheless, there may be considerable (but usually unsatisfactory) rises in the red cell counts. With very small dosages, the megaloblastic marrow may hardly alter at all; in these circumstances the peripheral response may be a mere flicker, sufficient perhaps only to halt a previous downward trend for a few days. With large single doses of the order of 30–40 μg. of crystalline B_{12}, 40–50 μg. of B_{12} concentrate or of a liver extract assayed at 30–40 μg., the marrow will probably remain normoblastic for the whole of the fifteen-day period or even longer; and in these patients the red cell responses in the peripheral blood will usually be greater than the expected response as calculated from the Della Vida and Dyke formula. These points are illustrated in Fig. 1.

In cases responding maximally with a normoblastic marrow throughout, the red cell response curve for the first fifteen days seems to follow a definite biphasic form; first there is a sharp rise starting on the second or third day and lasting three to four days, then there is a pause for two to three days and finally a second sharp rise starting on about the ninth day which gradually tails off (Fig. 2).

Marrow studies indicate that the first sharp rise is the sequel to a tremendous development of ripe (pyknotic) normoblasts. These cells all ripen within a short period of time and are clearly derived from the large accumulation of frustrated primitive cells of approximately the same age typically present in the severe case before treatment. By the sixth to seventh day, however, the marrow is relatively hypocellular and "empty". Ripe normoblasts are much less conspicuous, and the rise in the peripheral count is in consequence slowed down or almost halted. This deficiency of ripe cells in the marrow does not, however, last long, and the formation of a second generation of normoblasts results in a further rapid outpouring of cells and the second phase of increase in the peripheral blood.

When doses of liver or B_{12} are given sufficient to satisfy the requirements of an "average satisfactory" response only, it is likely that the first rise will be the only sharp one that is observed, and that the pause from the sixth to ninth day will merge into a less distinct and much less steep secondary rise. The response curve under these circumstances is typically sigmoid in shape (Fig. 3).

[1]The microbiological assay of these extracts has been kindly carried out by Dr. W. F. J. Cuthbertson of Glaxo Laboratories using *L. lactis Dorner* as the test organism, and in certain cases by Lederle Laboratories using *Lactobacillus leichmannii* 313.

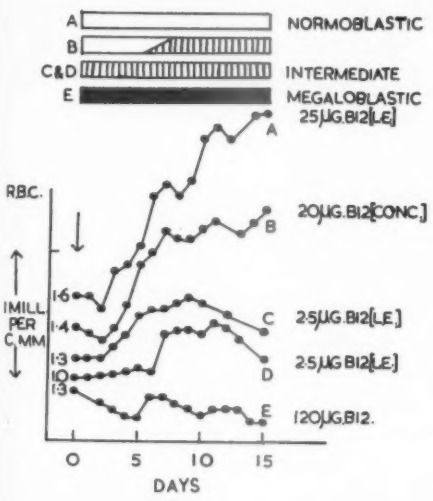


FIG. 1.

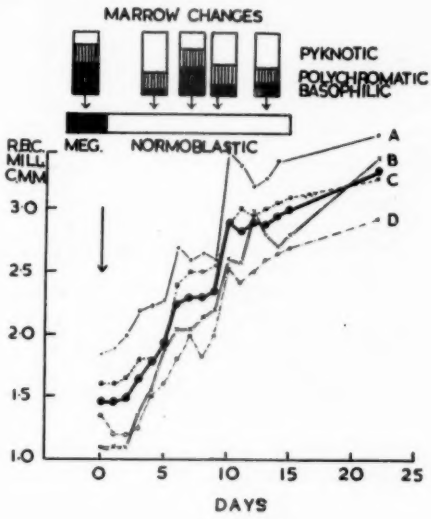


FIG. 2.

FIG. 1.—The bone-marrow changes and the initial red cell responses in 4 patients with pernicious anæmia (A–D), and in 1 patient with refractory megaloblastic anæmia (E), who were treated with single injections of crystalline vitamin B_{12}, vitamin B_{12} concentrate or with liver extracts of known vitamin B_{12} content. The bone-marrow changes are indicated in the rectangles at the top of the figure. The black shading indicates a megaloblastic bone-marrow, the "hatched" shading indicates an intermediate marrow, and the absence of shading a normoblastic marrow.

FIG. 2.—The initial red cell responses of 4 patients with pernicious anæmia in whom erythropoiesis remained normal for at least fifteen days after the start of treatment. The proportions of basophilic, polychromatic and pyknotic erythroblasts, as revealed by serial marrow punctures, are also given. The basophilic component includes hæmocytoblasts, pronormoblasts (or promegaloblasts) and early basophilic normoblasts. *Patients A and C* received single injections of liver extract; the vitamin B_{12} content of the doses given was assayed as 125 μg. and 30 μg. respectively. *Patient B* received 20 mg. folic acid daily. *Patient D* received a single injection of 30 μg. crystalline vitamin B_{12}. The dark continuous line is the average of the four responses.

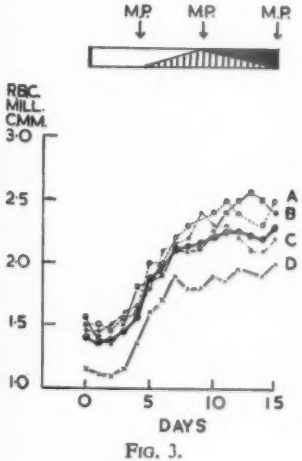


FIG. 3.

FIG. 3.—The initial red cell responses of 4 patients with pernicious anæmia in whom normoblastic erythropoiesis was not maintained for the whole of the fifteen-day period. *Patient A* received a single injection of 20 μg. vitamin B_{12} c. *Patients B and D* received single injections of 20 μg. vitamin B_{12} concentrate. *Patient C* received a single injection of liver extract; the vitamin B_{12} content was assayed as 2·5 μg. The dark continuous line is the average of the four responses.

The marrow changes are indicated above. M.P. denotes a marrow puncture. The black shading indicates a megaloblastic marrow, the "hatched" shading an "intermediate" marrow, and the absence of shading a normoblastic marrow.

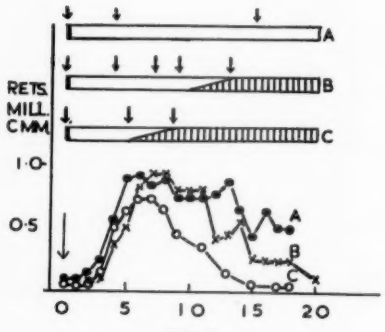


FIG. 4.

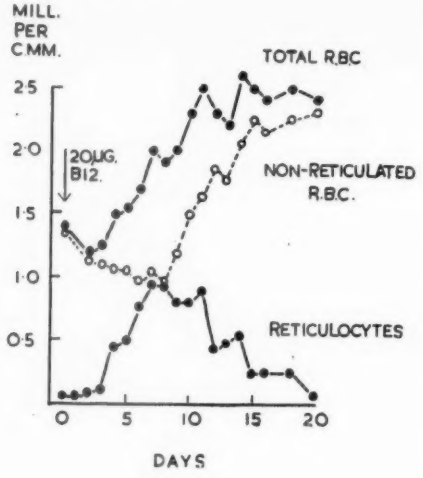


FIG. 5.

FIG. 4.—The form, height and duration of the reticulocyte responses in relation to the bone-marrow changes in 3 patients (A, B, C) with pernicious anæmia treated with folic acid, crystalline vitamin B_{12} or vitamin B_{12} concentrate respectively. The reticulocyte counts are expressed in absolute numbers. *Patient A* was treated with 20 mg. folic acid daily. Erythropoiesis remained normoblastic throughout the period of observation. *Patient B* received a single injection of 20 μg. crystalline vitamin B_{12}. Reversion to megaloblastic erythropoiesis was present by the thirteenth day. *Patient C* was treated with 20 μg. vitamin B_{12} concentrate. Reversion to megaloblastic erythropoiesis was present by the eighth to ninth day. The arrows indicate the dates of sternal punctures. The "hatched" shading denotes an "intermediate" marrow, and the absence of shading a normoblastic marrow.

FIG. 5.—The reticulocyte response, initial red cell response and non-reticulated red cell count in a patient with pernicious anæmia treated with crystalline vitamin B_{12}.

The reticulocyte count and the red cell count paralleled one another until the seventh day. The counts diverged after this date as the reticulocytes became transformed into mature red cells. The non-reticulated count started to rise after the seventh day.

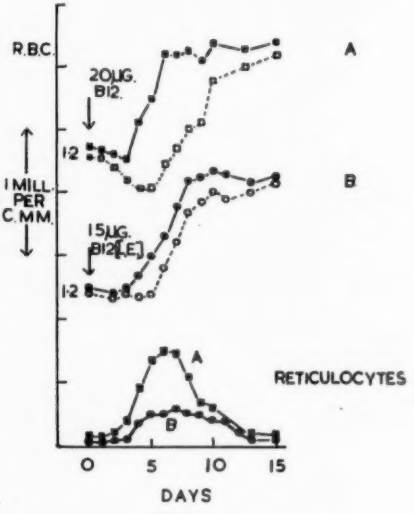


FIG. 6.

FIG. 6.—The reticulocyte responses, initial red cell responses and non-reticulated red cell counts of two patients (A, B) with pernicious anæmia, treated with single injections of vitamin B_{12} and liver extract respectively. Continuous lines: Total red cell counts. Interrupted lines: Non-reticulated red cell counts.

The sharper response of patient A was associated with a higher reticulocyte curve and a more prolonged reticulocyte life, compared with the changes observed in the case of patient B.

The reticulocyte response to liver therapy has been extensively studied for many years. Riddle's paper (1930) is particularly noteworthy. Working with large single doses of liver extract, he studied the absolute numbers of reticulocytes in the circulation and came to the conclusion that all the new cells appearing in a patient's blood during the initial response to treatment with liver were, in fact, reticulocytes. If this view is correct, and we believe that it is, almost as much information should be obtainable by studying the reticulocyte response in the first few days of therapy as by studying the rate of rise of the red cells themselves.

Nevertheless, most workers using reticulocyte percentages as criteria have come to the conclusion that there is no reliable correlation between the percentage reticulocyte response and the rise in red cells. One reason for this is clearly the assessment of reticulocyte responses as *percentages*. This method of assessment is convenient and will certainly demonstrate small differences, but it has its drawbacks. For instance, a reticulocyte count of 50% with the total red cell count at 1 million per c.mm. and a 25% count at the 2 million level represent the same *total* number of reticulocytes; in both cases, 500,000 per c.mm. In the above example there is a temptation to believe that the 25% response indicates a less intense marrow effort than does the 50% response, which is simply not the case. Another objection to plotting the reticulocyte response as a percentage is that the scale of references is altering all the time; at the end of a fifteen-day period the red cell count may have been almost doubled, so that 5% of reticulocytes at the end of the period corresponds with 10% in the early days of the response.

A number of factors probably contribute to the form and duration of the reticulocyte response. Firstly, the primitiveness of the marrow—in the most severe cases of pernicious anæmia many basophilic primitive promegaloblasts are present and the marrow as a whole is usually tremendously hyperplastic. When a marrow of this type is permitted to develop by the administration of a sufficient quantity of B_{12}, there is a tremendous surge of activity and many normoblasts mature within a day or so, and a tremendous outpouring of reticulocytes results. The first factor which controls the reticulocyte response is thus the marrow—how hyperplastic it is, and how homogeneous. The next factor is, of course, the potency of the material administered in relation to the patient's requirements. This will determine the response of the marrow which in turn will be reflected in the number of reticulocytes that are formed and the speed with which they appear in the peripheral circulation.

Then, of fundamental importance in controlling the form of the reticulocyte response curve, particularly its height and width, is the speed with which the reticulocytes ripen in the peripheral circulation. This depends, at least in part, on their maturity as they are delivered. It seems that the more vigorous the response the more immature are the reticulocytes which appear in the blood stream and in consequence the more prolonged is their average life-span. Ripening may also depend on humoral ripening factors, in which category perhaps B_{12} and liver extracts themselves may be included. This is, however, rather a matter for speculation at the moment.

The typical reticulocyte response curve is asymmetrical, the initial rise being steeper than the subsequent fall. The better and more sustained the marrow response (the more potent the preparation given) the more asymmetrical are the curves. A rise followed by a relatively quick fall to relatively low levels means that the marrow is soon ceasing to form many new cells, and the reticulocyte count will fall as soon as those cells initially delivered ripen (Fig. 4).

It is instructive to calculate the non-reticulated red cell count by subtracting from the total count the reticulocyte count in absolute numbers, and to plot the totals separately. If this is done, it will be seen, firstly, that the total red cell count and the reticulocyte count rise in a strikingly parallel fashion, strongly suggesting that the total cell rise, for at least the first seven days, is wholly due to increments of reticulocytes. Secondly, it becomes clear that the non-reticulated count does not rise until several days after the start of the reticulocyte rise (Fig. 5).

The ripening time of reticulocytes as illustrated in Fig. 5 seems to be as long as five days. In most cases it appears to be three to four days. It may, however, appear to be even shorter than this. In these cases the total reticulocyte count may be disappointingly low, although sustained, and yet the total red cell rise for the whole fifteen-day period may be quite good (Fig. 6). These differences can be partially explained on the basis of different degrees of immaturity of the cells as they are delivered from the marrow, depending upon the intensity of the response. It would be premature to speculate as to whether there was any difference in the behaviour of patients treated with liver extracts and those treated with B_{12} preparations in this respect.

Conclusions

(1) It is necessary to give large doses of vitamin B_{12} or liver extract to patients with pernicious anæmia, if it is desired to maintain a normoblastic marrow for fifteen days following a single injection. Doses of the order of 30–40 μg. of crystalline B_{12} or 40–50 μg. of B_{12} concentrate are required, or an injection of a liver extract assayed to contain 30–40 μg. B_{12}. In patients thus treated the red cell responses tend to occur in two phases, separated by a relative pause at about the sixth to ninth day.

(2) So-called "average satisfactory" responses can be obtained in the majority of patients with half the quantities of B_{12} or less than are mentioned above. In these cases, however, the marrow will have become megaloblastic again well before the end of the fifteen-day period, and the second phase of red cell response will be diminished. The potency of an extract can in fact be quite reliably assessed clinically by studying the changes it produces in the bone-marrow.

(3) It seems that all the red cells produced as a response to the administration of an adequate dose of liver extract or B_{12} probably enter the blood stream as reticulocytes, for the rises in reticulocyte numbers and red cell numbers closely parallel each other in the early stages of the response.

(4) The form of the reticulocyte response curve is determined by several factors: the hyperplasia in the marrow, the potency of the material administered in relation to the patient's requirements, the degree of immaturity of the reticulocytes as delivered into the blood stream and the rate at which they ripen therein. It is this rather complicated relationship which limits the value of the reticulocyte response as a means of assessing clinically the potency of liver extracts and vitamin B_{12}.

References

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Clinical Section

President—W. A. BOURNE, M.D.

[*March* 10, 1950]

Endarteriectomy in the Treatment of Chronic Endarteritis Obliterans of the Limbs and Abdominal Aorta[1]

By HENRI REBOUL, M.D., *Paris*, and PIERRE LAUBRY, M.D., *Paris*

VASCULAR surgery had its first phase of great activity at the end of last century and at the beginning of this one.

In several important publications between 1905 and 1911 Pierre Delbet [1 and 2] reviewed the earlier techniques for the "disobliteration" of arterial thromboses.

The first, ascribed to Sévéréanu [1, p. 157] dates from 1894 and was called "Désoblitération par Cathétérisme Artériel". The thrombus was broken up and detached by a gum-elastic urethral catheter introduced through the orifice of a main obliterated artery exposed on the section of amputation of a gangrenous limb. By this means amputation at the site of election was successfully substituted for an amputation through the thigh.

In 1901 Guinard [1, p. 158] used long forceps to remove the clot while Martin [1, p. 158] noticed the re-establishment of the collateral circulation after this procedure.

Disobliteration by catheterization through one or several limited arteriotomies was first performed by Lejars [1, p. 152] in 1902, and in 1911 Delbet wrote: "The easiest operation that can be done to cure arterial obstruction is incision of the artery, extraction of the thrombus and closure of the vessel," but, he added: "In thrombosis due to endarteritis one can hope for but little from recanalization of the artery. On the impaired walls the clot reforms with a distressing rapidity."

These attempts were almost completely forgotten as was much excellent work on arterial suturing, on arterio-venous anastomoses, on vascular grafting, on thromboses, and on the part played by the white cells on surfaces denuded of endothelium and on the extraordinary power of regeneration of the vascular endothelium [1].

Since 1911 there have been reported only a few isolated cases of recanalizations of old arterial thromboses. To J. C. dos Santos and R. Leriche [3, 4] must be given the credit of studying this technique again whilst making use of arteriography and anticoagulants. In 1947, in the presence of our teachers Charles Laubry and Louis Bazy, they kindly showed us their technique by operating on three of our patients assisted by Jacques Huguier and ourselves.

Through two short longitudinal arteriotomies of 2 to 3 cm. across the upper and lower limits of a segmental arterial obstruction, previously located by arteriography, J. C. dos Santos introduced helicoid scrapers, small spatulæ, malleable stylets, curettes and forceps to dislodge the thrombus and extract it. The operation was completed by an arteriography for control, flushing with saline containing heparin and suture of the two original incisions and sometimes of one or two supplementary incisions. During the operation heparin was administered intravenously to bring the coagulation time to above fifteen minutes and was continued for two or three days.

With Jaques Huguier we have performed this operation four times. We sent another patient to J. C. dos Santos in Lisbon where he operated on him.

J. C. dos Santos believed that the chief indication for this technique was in segmental obstruction due to old embolus. The failures in this treatment have been attributed to the severity and long duration of the lesions. In fact, however, instruments can only be introduced with ease through the first 2 or 3 cm. of their passage along arteries. Afterwards, especially in the case of endarteritis obliterans of old standing, with very sclerotic or atheromatous parietal lesions, the instruments become engaged between the coats of the vessels, tear and even pierce them at places impossible to locate. These findings caused us to abandon this method.

On October 21, 1947, we performed an operation which our teacher Professor Louis Bazy [5] described in outline with the immediate end-results and which was called "Endartériectomie Dèsoblitérante".

[1] This work was undertaken under the scientific direction of MM. Charles Laubry and Louis Bazy in the hospital services of MM. Louis Bazy, Mouquin, Thoyer-Rozat and Pierre Huet and until December 1948 in collaboration with Jacques Huguier.

The Operation of Disobliterative Endarteriectomy [1]

Indications.—At the present time the indications for recanalizing endarteriectomy should be restricted to cases of arteritis of non-acute form and those not compensated by a sufficiently well-developed collateral circulation. For this reason we believe that before undertaking an operation of any kind a thorough investigation should be made in all cases of chronic arteritis and a prolonged course of medical treatment given for any general metabolic disorder. This should include rest, physical and mental, analgesics and sedatives, and repeated infiltrations of the lumbo-sacral sympathetic ganglia with 30 c.c. of 1/200 novocain to which 500 mg. of sodium nicotinate have been added. Endarteriectomy should only be considered after failure of a prolonged treatment by these methods. Obviously cases should not be operated upon when there are active and progressive lesions especially if these are present in several arteries. A good and very extensive arteriography into the free circulation is in our opinion practically indispensable to estimate these factors with sufficient accuracy.

Technique.—The coagulation time measured on a vaselined slide is taken every ten minutes throughout the operation. It is necessary to inject sufficient doses of heparin to bring it to fifteen minutes during the time of exposure, incision and clearing of the artery and to bring it to above thirty minutes as soon as the clamps have been tightened preparatory to suturing. We have not found a standard dose. The initial dose is about 25 mg. and the subsequent doses from 25 to 60 mg. repeated every twenty to forty-five minutes.

Incision.—The methods of approach that we use for the limbs correspond with those customarily used and should give a good exposure of the whole thrombosed arterial segment with several centimetres at either end. For the femoral and upper half of the popliteal we use the single incision advocated by A. K. Henry and taught in France by Leriche [4].

Clearance and incision of the artery.—A strip 2 to 5 mm. wide on the superficial aspect of the artery must be completely cleared of all adipose cellular tissue and of all small venules and arterioles which sometimes cross it. The adventitia should be carefully preserved. Important collaterals are treated similarly and a guide suture placed under them. Above and below the obliterated segment a Louis Bazy clamp, rubber shod, is placed on the artery but it is not tightened at this stage (Fig. 1).

The artery is now opened longitudinally with a scalpel for a distance of 4 to 6 cm. and the thrombus exposed. On the lips of this incision a plane of cleavage is sought with a pair of closed blunt scissors curved on the flat (Fig. 2). It is generally found between the external elastic limiting layer and the media. The necrosed media, the internal elastic limiting layer and the intima adhere to the thrombus and are removed with it. Only the living external elastic limiting layer and the adventitia are retained. Thus the operation in its separation of the dead from the living tissues may be likened to a sequestrectomy. The plane of cleavage is next defined by blunt dissection around the thrombus and to its upper and lower limits, the arterial incision being progressively extended with the scissors over its whole extent (Fig. 3).

At the orifice of each collateral the plane of cleavage is momentarily lost as the thrombus extends for a few millimetres into the collateral. When this has been disengaged either by gentle traction or by separation with a blunt probe introduced into the collateral, blood begins to flow from the liberated orifice. The collateral is then clamped with a Carrel's clamp or traction is made on the guide suture previously put in place.

It only remains to complete the endarteriectomy above and below by cutting through the inner arterial coats in a healthy zone, making sure that no fringe is left projecting into the lumen. Before doing so the Louis Bazy clamps at each end of the arterial incision are tightened. They are momentarily released before the suture is commenced to confirm the completeness of the disobliteration as shown by a rhythmic flow of blood from the proximal end and a continuous one from the distal end. This also serves to wash away any debris.

After completion of the endarteriectomy the exposed bluish-white limiting layer has a pearly appearance upon which are points of blood oozing from the vasa vasorum. Here and there a few islands of muscle-coat remain. These are only removed if not too adherent.

Throughout these manipulations the arterial bed must be very frequently irrigated with normal saline containing 500 mg. of heparin per 100 c.c. Gloves, instruments and suture material are kept moistened with the same solution throughout the stage of arterial suture.

Arterial suture.—Black silk 00000 is used either mounted on atraumatic Decknatel needles, straight or curved, held in a modified ophthalmological needle-holder; or the special needle devised by us may be used (Fig. 4). Two layers of continuous suture are employed. The first takes the external limiting layer and the adventitia and everts the edges. The stitches are introduced about 1·5 mm. apart. This may be done over a fine rubber tube which also serves for perfusion with heparin solution. It is withdrawn as the suture line is completed.

[1] A film was shown illustrating the operative technique, arterio-phlebographic control and post-operative results.

A second continuous suture taking adventitia and some areolar tissue buries the first (Fig. 5). The clamps are now removed from the collaterals, the distal end of the artery and the proximal end in that order. The slight ooze from the suture line ceases as the suture tightens under the influence of the returning intra-arterial blood pressure. A few interrupted reinforcing stitches may be required here and there.



FIG. 1. — Louis Bazy clamp. This clamp is the least traumatizing, the easiest to place and the least hampering during suture of the artery.



FIG. 2.—Defining a plane of cleavage between the internal coats, to be resected with the thrombus which they enclose and to which they adhere, and the external elastic limiting layer which is to be retained with the adventitia.



FIG. 3. — The inner surface of the external elastic limiting layer is thoroughly exposed and carefully examined. Endarteriectomy will only be proceeded with when this layer is viable and of normal appearance.



FIG. 4.—Henri Reboul needle. The length of the handle is adjustable. The needle is interchangeable. Its open eye exactly accommodates 00000 black silk.



FIG. 5.—On the *right* the artery is not yet sutured. On the *left* the second layer of suture is in progress. In the *centre* a short segment of the first layer of suture has not yet been invaginated by the second layer.

Closure of the wound.—Hæmostasis is carefully attended to. A corrugated rubber drain is placed near but not touching the artery. The wound is closed in layers.

Post-operative care.—Though blood-loss at operation is very slight, fluid and protein loss should be made good by transfusion. Intravenous heparin is continued meanwhile and for

the next three or four days to keep the coagulation time at about fifteen to twenty minutes. Thereafter heparin is administered subcutaneously in diminishing doses until the coagulation time returns to normal about the twelfth day.

Results of Operation

Either immediately or in the course of forty-eight hours peripheral pulses become perceptible and the skin becomes warm and of good colour. Very often, when before operation it seemed certain that even in the event of success, one or several toes would require to be amputated, we have been happily surprised to see their teguments dry, blacken and be thrown off and complete healing to follow. In every case these patients obtain complete relief from pain from the first night following operation, however severe it may have been previously.

On several of our specimens Professor Champy and Mademoiselle Demay were able to demonstrate that from the time that the arterial circulation was re-established, the denuded surface of the external limiting layer became rapidly and completely lined by a layer of leukocytes. From the collaterals and from the upper and lower ends of the main artery, the intima grows again, progressively replacing the lining of leukocytes. It appears to be fully reformed after about a month (Fig. 6).



Fig. 6A.



Fig. 6B.

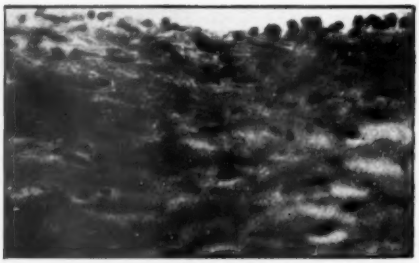


Fig. 6C.

Fig. 6.—Post-mortem specimen of artery obtained one month after disobliterative endarteriectomy of the upper femoral artery and a few hours after a similar operation on the lower femoral and popliteal arteries. (Death was due to shock.) The artery is opened and flattened out. (A) *Left*: Segment of unoperated iliac artery. The upper limit of the endarteriectomy is clearly visible. *Centre*: Long segment of femoral artery endarteriectomized one month previously. Only the external elastic limiting layer and the adventitia had been preserved. The arterial wall has regenerated to a normal thickness. The new intima has a normal appearance and has completely covered the suture. *Right*: Short segment of lower femoral artery endarteriectomized a few hours previously. (B) Section (low power) at the junction of the two endarteriectomies seen on the right in (A) above. Note regenerated intima on left and recently denuded external elastic limiting layer on right. (C) Section (high power) showing leukocytes lining the recently denuded external elastic limiting layer. (Microscopical preparation by Professor Champy and Mademoiselle Demay.)

Post-operative arterio-phlebography in the free circulation shows restored permeability of the endarteriectomised segment and a distinct improvement in the rate of appearance of the opaque medium in the distal arteries and in the veins.

In spite of these reassuring observations we have never been led to believe that arteritis, a systemic disease, could be considered cured following such local reconstructions. Later ischæmic complications have, up to the present, rarely been relapses but have occurred at other sites. Moreover, even when new thromboses have occurred at the original site or elsewhere, many of the patients have maintained a satisfactory clinical improvement. This has doubtless been due to the vasodilator effect of the resection of the intra-mural nerve elements in endarteriectomy.

TABLE I.—DISOBLITERATIVE ENDARTERIECTOMY. RESULTS

Site	No. of operations	Remained permeable; complete relief of symptoms	Deaths; post-operative and remote	Reobliteration early and remote
Aorta	19	8	7	4
Ileo-femoral	6	3	1	2
Femoral	29	14	1	14
Femoro-popliteal	20	10	2	8
Popliteal	11	6	0	5
Femoro-popliteal and post. tibial ..	3	0	0	3
Post. tibial	3	1	0	2
Brachial	2	2	0	0
Total	93	44	11	38

TABLE II.—DISOBLITERATIVE ENDARTERIECTOMY. ANALYSIS OF CASES WITH SUBSEQUENT REOBLITERATION

Site	No. of cases	Improved, good and moderate	No improvement	Amputation
Aorta	4	3	1	0
Ileo-femoral	2	1	1	0
Femoral	14	10	1	3
Femoro-popliteal	8	4	3	1
Popliteal	5	2	3	0
Femoro-popliteal and post. tibial ..	3	2	1	0
Post. tibial	2	1	0	1
Brachial	0	0	0	0
Total	38	23	10	5

93 endarteriectomies and the twenty-eight months of observation since the first operation are not sufficient to form an opinion on the future of such a new technique.

However, we believe they have proved that with modern anæsthetics and methods of averting shock :

(1) Long arterial sutures on the abdominal aorta, the iliacs and main arteries of the limbs can be made with reasonable safety.

(2) Resection of the intima, the sub-endothelial layer, the internal elastic limiting layer and the muscular layer does not weaken the arterial wall to a dangerous degree, provided that the external elastic limiting layer which is alone retained with the adventitia is in a healthy condition.

(3) The regeneration of the artery after endarteriectomy is rapid and of good quality; this applies to the intima as well as to the total thickness of the wall.

(4) The resection of the nerve elements included in the internal coats accounts for an effective neuro-endarteriectomy as indicated by clinical results and arterio-phlebography in free circulation over the whole extent of the limb.

(5) Using heparin only partially solves the problem of clotting during and after operation. This difficulty still considerably limits the indications for this operation in cases other than those where the progress of the arteritis menaces life or necessitates amputation.

It seems justifiable to conclude that the study of this operation, supported by long clinical and biological observations on thousands of patients suffering from arteritis, and by the comparison of several hundred arterio-phlebograms furnishes weighty evidence in favour of a single pathological origin of chronic arteritis and of spontaneously occurring aneurysmal dilatations of non-specific origin.

Many ætiological factors, psychic, endocrine, allergic, or in the nature of hetero- and auto-intoxications are capable of initiating vasomotor disturbances which end in slowing down the capillary circulation. Depending on the intensity of the reaction on the vasa vasorum, this phenomenon results in changes in the arterial wall which vary between œdema, leukocytic infiltration and ischæmia predominating in the media.

Lesions of an inflammatory character progress towards sclerosis. Those of an ischæmic character progress either towards necrosis and dilatation if they are very active, or towards the deposition of lipoids and calcium if less acute. Changes in the intima secondary to such

degenerations of the media predispose to the formation of intra-arterial clotting but are not alone sufficient to provoke it. We believe that this thrombosis may be precipitated by variations in the clotting time occurring under the influence of many different factors among which exogenous and endogenous toxæmia are particularly worth mentioning. Lastly, vasomotor disturbances appear to be kept up by lesions of the arterial wall. They progress in bouts which are just as variable in their intensity as in their frequency.

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Mr. A. Dickson Wright: Dr. Reboul has shown in the film very adequately the technique of this valuable operation and has developed with Dr. Bazy the method recommended two years ago in London by Dr. dos Santos of Lisbon in his Hunterian oration. It is a remarkable thing that these arteries, sometimes solid cords of long standing, still have a medial coat from which a new artery can be constructed with heparin to prevent thrombosis until the media is lined with a new intima. The patient shown was relieved of claudication and impending gangrene and it is likely that many a leg will be saved by this new method which should be tried in any case with encouraging arteriograms.

Mr. Peter Martin: I must congratulate Dr. Reboul on his magnificent contribution to vascular surgery. It is interesting to note that the results have been very much better where the larger arteries have been treated than where smaller vessels are concerned. My own opinion is that one could do quite a lot with the larger vessels, but as soon as the smaller vessels are at fault any operative treatment is nearly always followed by thrombosis.

I agree entirely with Dr. Reboul's remarks about heparin which does not seem to be the final answer to the thrombosis, although it is certainly a tremendous help in vascular surgery.

It would seem to me that in diffuse arteriosclerosis endarteriectomy would be of doubtful benefit as the disease is so generalized, but where the femoral artery particularly is blocked especially in younger people, a condition which has not a very good prognosis, the operation might be of great value.

Mr. J. B. Kinmonth: The success of this operation rests upon whether the vessel stays patent or becomes blocked by a new clot. Dr. Reboul's results show a worth-while proportion of successes and the patient whom he has shown us is a convincing proof of the value of the operation.

My experience of the operation is limited to one patient, a man of 30, with a four-inch clot in the femoral and popliteal arteries causing claudication at a hundred yards. This had not been relieved by sympathectomy, as so often happens when the larger vessels are involved. It was impossible to insert a homologous arterial graft as intended because the disease was found to extend further down the popliteal artery than the arteriogram had suggested. Endarteriectomy was done through three short longitudinal incisions. A plane of cleavage was formed using a Watson-Cheyne dissector and the yellow clot attached to part of the wall was removed. A surprisingly smooth surface remained inside the artery which was sewn up with an atraumatic needle and five zero silk.

The vessel pulsated well after the procedure was completed. One of the new coumarol anticoagulants has been given since operation but it is too early to say whether permanent patency has been achieved.

The two points of interest were that the actual endarteriectomy was easy, leaving a smooth surface, and that the operation could be done without instruments specially designed for it.

One difficulty, and I think an important one, is that time and care must be spent in avoiding damage to collateral vessels.

We are most grateful to Dr. Reboul for a very stimulating hour and congratulate him on his important work and most interesting film.

Section of Dermatology

President—W. N. GOLDSMITH, M.D., F.R.C.P.

[*January* 19, 1950]

Psoriasis Arthropathica.—H. W. BARBER, F.R.C.P.

Mr. M., aged 52. This patient is a remarkable example of the variety of psoriasis arthropathica in which the affection of the joints takes the form of intermittent or paroxysmal hydrarthrosis without permanent damage to the joint structures ("palindromic rheumatism" of Hench and Rosenberg, 1941). This variety is, I think, much rarer than (1) that in which the arthritis is of the rheumatoid type (atrophic arthritis; arthritis deformans), and (2) that in which the arthritis is primarily gouty with secondary osteo-arthritic changes in the joints. It is not, however, so rare as that described by Bauer and Vogel (1931) and by Shlionsky and Blake (1936) in which such severe deformities of the extremities occur owing to osteoporosis that the hands and feet may be shrunken to half their normal size. Dr. L. Forman showed a case of this kind before the Section in November 1948. I agree with Cecil that in the majority of patients with psoriasis arthropathica the arthritis is characteristic of arthritis deformans, although the early and marked involvement and deformity of the terminal interphalangeal joints of the fingers and toes with severe psoriatic changes in the corresponding nails is rather a special feature.

Family History.

Paternal side.—Grandfather reputed to have some "skin defect". Grandmother nothing significant known. Both died of cancer. Father ? eczema. Died of prostatic cancer. One uncle out of three male and one female sibs had severe hay-fever, and his niece has had it since childhood. Her mother has ? eczema.

Maternal side.—Both grandparents died comparatively young of tuberculosis (?). Mother still alive. At age of 40 severe generalized outbreak of an eruption (? psoriasis ? eczema), which was treated with arsenic and sour milk and lasted three months. During the last fifteen to twenty years scaly patches on the legs at times. She had "rheumatism" for many years and eventually acute arthritis for which she was given injections of gold five years ago with benefit. One of her sisters has asthma.

Personal History.

Age 13, Hayfever began (June and July). 21–25, Reached its maximum and at times was accompanied by asthma. 30, Hay-fever diminishing. Psoriasis appeared first on the scalp. 32, Tonsillitis with quinsy. 33–42, Psoriasis gradually increasing. 43–47, Psoriasis extending over the trunk. 48, Finger- and toe-nails involved.

Given hog's stomach and mercurial injections. Nails improved, but not the eruption. For several years the knees had swollen periodically for short periods, and at the age of 50 there occurred severe attacks of intermittent hydrarthrosis in the knees, ankles, and toe-joints accompanied by tachycardia. Treatment with benadryl had no effect, but there was some benefit from injections of collosol calcium with vitamin D.

The attacks of intermittent hydrarthrosis and tachycardia were followed by copious diuresis ("urina spastica") indicating the fluid retention that obtains during acute attacks of allergic symptoms (cf. migraine). In September 1947 he consulted Dr. H. S. Barber of Buxton who said that the joint affection was neither rheumatoid arthritis nor gout, but allied to allergic conditions. He had previously seen Dr. O. Brenner about the attacks of tachycardia. No structural disease of the heart was found, the attacks being clearly paroxysmal tachycardia.

The patient's medical attendant—Dr. Burns Selkirk—on his own initiative at this time began treatment with arsenic as Fowler's solution in dosage of 2–6 minims thrice daily. With this treatment, recommended to him by Dr. C. W. Buckley of Buxton, he had previously cured a lady with a "peculiar crippling rheumatism".

The arsenical treatment effectively abolished the intermittent hydrarthrosis and the psoriasis greatly improved. The second course ended 9.12.47, and on 6.1.48 there was a relapse which responded to another course.

In August 1948 another attack of tonsillitis occurred which was treated with a sulphonamide and penicillin.

Mr. A. J. Moffett was later consulted, but did not advise operative treatment.

The patient has kept a careful and illuminating graph which illustrates very clearly the waxing and waning both of the hydrarthrosis and the psoriasis. It will be seen that as a rule the two conditions proceed *pari passu*, but there was an exception in September and October 1948, when the hydrarthrosis was severe and the psoriasis mild.

Although exacerbations and remissions are of course characteristic of the intermittent hydrarthrosis and of the psoriasis in this variety of psoriasis arthropathica, which fact makes it difficult to assess the value of any particular line of treatment, it would appear from the graph that, as Garrod and Evans (1924) found in their cases, arsenic has a remarkable effect. Garrod remarks that "it is the drug of chief value in cases of intermittent hydrarthrosis".

Investigations.—Radiograms of the teeth and jaws (1946) revealed nothing abnormal except a piece of retained root. In spite of the attacks of tonsillitis and quinsy Mr. Moffett evidently did not regard the tonsils as being chronically infected, and the attacks do not appear to have provoked exacerbations. At my request radiograms of the affected joints were taken (Dr. H. Black).

His report was: "The appearances of the knee-joints are normal. There is no erosion and no osteophyte formation. At both great toe joints there is osteo-arthritis. There is some periosteal thickening in the first phalanx of the right second toe."

The blood uric acid was reported to be over 16 mg.%—an almost incredibly high figure, which I cannot credit.

The second estimation gave serum uric acid = 4·6 mg./100 ml.

Blood count within normal limits.

Sedimentation rate: 10 mm. in the first hour.

Further treatment.—As Dr. Selkirk was rightly unwilling to continue treatment with arsenic indefinitely, I suggested the following (3.10.49): Sterogyl-15, two ampoules weekly for three weeks, and one weekly for six weeks: Syr. calcii chloridi B.P.C. dr. 2 bis die: Livogen dr. 2 bis die: Eucortone 2 c.c. intramuscularly twice or thrice weekly. This line of treatment, which is of value in some allergic cases, proved disappointing, so I suggested Stovarsol as an alternative to Fowler's solution, but this seems to have caused toxic symptoms and has been omitted.

Summary.—This then is a case of intermittent hydrarthrosis and psoriasis with a family history of hay-fever and ? eczema on the paternal side, and of arthritis (? rheumatoid), ? psoriasis ? eczema, and asthma on the maternal side, and with a personal history of severe hay-fever and sometimes asthma, and of paroxysmal tachycardia. It resembles two at least of the three cases of "arthropathia psoriatica" described by Garrod and Evans (1924) in the occurrence of intermittent hydrarthrosis with exacerbations of the psoriasis, and in the favourable response of both conditions to arsenic.

Discussion.—As regards the affection of the joints and periarticular tissue, the case corresponds to that described by Hench and Rosenberg (1941) under the term "palindromic rheumatism", which, although they note certain differences, is doubtless essentially the same as the "angioneural arthrosis" of Solis-Cohen (1911, 1914) and the "allergic rheumatism" of Kahlmeter (1939). In my opinion, too, it is identical with Garrod's (1910) primary intermittent hydrarthrosis.

Hench and Rosenberg discuss whether or not their palindromic rheumatism should be regarded as an allergic manifestation, and Prickman in the discussion following their paper thought "the evidence at present points away from an allergic basis". These observers seem to have been unaware of Garrod's experience of the value of arsenical treatment.

Dr. Parkes Weber's admirable paper (1946) on palindromic rheumatism should be consulted for a discussion of the condition and for a description of 2 cases in 1 of which the hip-joints only were involved and the patient suffered from Ménière's syndrome and recurrent attacks of iritis.

Whether one chooses to call these and allied symptoms "allergic" or not, there is one factor common to all, namely fluid retention with mobilization of fluid in the particular structure involved. This is true of eczema, urticaria, angioneurotic œdema, intermittent hydrarthrosis, rhinorrhœa, asthma, migraine and Ménière's disease. It is interesting to note that my patient has observed that when his psoriasis is at its worst weeping occurs on removal of the scales.

There is another point of great interest in 2 of the 3 cases described by Garrod and Evans, namely that the exacerbations of the arthritis and psoriasis were associated with irregularity of the menses or amenorrhœa, whereas during the remissions the periods were normal and regular. There was no record of the menstrual history in the third case.

I would suggest that we may explain some of the symptoms of this remarkable syndrome in terms of the countershock phase of Selye's "Alarm Reaction". As you know, in this phase the anterior pituitary is stimulated to secrete an excess of the adreno-cortico-trophic hormone (A.C.T.H.) at the expense of the growth, gonadotrophic, and lactogenic hormones. The diminution in the secretion of the gonadotrophic hormones would account for the irregular or absent menstruation. The production in excess of the "salt-and-water" hormones would cause the retention of fluid and the tendency to œdema in one tissue or another that periodically occur in these cases. Possibly, too, the two attacks of tonsillitis in my patient may be explained by the disintegrating influence of A.C.T.H. on lymphoid tissue.

We are often ignorant of the "alarming stimuli" that provoke these reactions, but in Garrod and Evans's first case it was clearly, as a rule, physical trauma.

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Dr. F. Parkes Weber: Case I.—I should like to make a remark on Dr. Barber's first very interesting case. In 1946 I published an article in the *Lancet* (ii, 931) on "Palindromic Rheumatism". The cases to which I referred were not of the psoriasis and rheumatoid arthritis type, that is, none of them were cases of psoriasis arthropathica or arthropathia psoriatica. In the second of the "complicated" cases which I described on page 933 (a man aged about 60) a great many specialists had been consulted, and it was afterwards the subject of a communication by Dr. E. G. L. Bywaters at the Annual Meeting in 1948 of the Association of Physicians of Great Britain and Ireland. Dr. Bywaters demonstrated that in that patient some of the lesions showed the microscopical structure of "necrobiotic nodules of the rheumatoid arthritis type" and he came to the conclusion that the case was not one of true palindromic rheumatism except in the symptomatic sense of the term, but that it was a case of rheumatoid arthritis simulating palindromic rheumatism. He worked this out very well and later in New York at a congress on rheumatism he called it a palindromic variant of rheumatoid arthritis (cf. *Brit. med. J.*, 1949 (ii), 157). I suppose that would suit Dr. Barber's views very well.

I am very doubtful whether palindromic rheumatism is a disease in itself and I am rather in favour of Bywaters' term, a palindromic (that is, recurrent) form or variant of rheumatoid arthritis.

Vitiligo with Migraine.—H. W. BARBER, F.R.C.P.

A. W., boy aged 9.

History.—Attacks of severe right-sided migraine began in the summer of 1948. Shortly afterwards vitiligo appeared on the right side of the face only. Dr. F. M. R. Walshe was consulted about the migraine early in 1949. At the time of onset the child was in a state of incertitude and tension because he was behindhand in his school-work and knew that he might be sent to a boarding-school.

I first saw the patient 28.7.49. At that time the vitiligo—depigmentation with surrounding hyperpigmentation—involved the outer parts of the eyelids and extended downwards on the cheek towards the angle of the mouth. The eyelashes were depigmented on the affected parts of the eyelids. The configuration of the descending patch on the cheek recalled that of morphœa "en coup de sabre". Apart from his migraine the boy appeared physically well, although very highly strung.

After conversation with his mother it was clear that he was very unhappy at a boarding-school because he hated being away from home. He had no objection to a day-school. His mother—rightly, I think—attributed his frequent attacks of migraine largely to nervous tension and I considered it likely that this was also responsible for his vitiligo.

I had no hesitation in advising his removal from the boarding-school, and his transference to a suitable day-school in London. The boy was at once informed of my decision. Improvement in the vitiligo was manifest within a month, and it almost disappeared during his first term at the day-school where he was quite happy.

I saw him again 20.12.49. The eyelashes are still depigmented on the outer part of the eyelids. Only faint traces of the vitiligo remain on the cheek. He has had a few attacks of migraine when excited or apprehensive, but much less frequently and severely.

The association of alopecia areata and migraine is not very uncommon, but I do not remember having seen a case of unilateral vitiligo with migraine before. I have discussed the case with Sir Charles Symonds. His comment was: "It is to me entirely understandable that psychological stress should have its effect upon the hypothalamus and cause symptoms of this kind."

Pemphigus Vegetans treated with Aureomycin.—H. W. BARBER, F.R.C.P., and ALLAN YORKE, M.R.C.S., L.R.C.P.

J. C., Petty Officer, aged 33.

This patient was first seen by Dr. H. W. Barber in September 1949, with an eruption involving the chin, axillæ, pubis, groins and internatal cleft which was described by his medical officer as consisting of bullæ, the largest being "the size of a grape". At the above sites were clustered vesicles and solitary plump bullæ arising from normal skin, together with a few indolent moist vegetative lesions at the right axilla and groins.

Dr. Barber wrote: "The eruption is a variety of the pemphigus group and is of the type that might very well become pemphigus vegetans in the flexures."

Within two weeks the patient had developed typical multiple vegetative lesions together with multiple bullæ and painful erosions of the buccal mucosa.

He was admitted to the East Surrey Hospital and treated as follows:

(1) *Sulphapyridine.*—1 gramme four-hourly until 117 grammes were given. He improved steadily—after an initial lag period of fourteen days—but relapsed completely within seven days of the drug being withdrawn. He exhibited no toxic symptoms and the blood picture, which was normal, remained so.

(2) *Stovarsol.*—6 grains after breakfast and 4 grains after the evening meal in courses of three days—separated by three-day intervals. Again he improved only to relapse after the tenth course despite the fact that the stovarsol was continued. He displayed no intolerance and there was no depression reflected in his blood picture—he was given anahæmin throughout.

The deterioration continued and sulphapyridine was exhibited but he was now intolerant with violent vomiting and anorexia.

It was therefore decided to treat him with aureomycin, one capsule (250 mg.) twice daily. The response was prompt. Within four days the skin was clear and within seven days the buccal mucosa was of normal appearance.

He has now been treated for twenty-two days. (One ampoule twice daily for fifteen days and three ampoules daily for seven days.) There have been no toxic symptoms neither has relapse taken place.

POSTSCRIPT (July 1950).—This patient relapsed within three weeks and despite a further course of aureomycin (5,000 mg. in twenty-four days) he showed no improvement.

Another patient treated along similar lines with aureomycin made a prompt and complete initial response only to relapse within four weeks.—A. Y.

Dr. C. H. Whittle: We have had a man with pemphigus vulgaris who was also treated with sulphapyridine without effect. We then gave aureomycin in doses of 2 grammes daily, and after the first forty-eight hours he felt much better and the blisters ceased to appear. This good result lasted five or six days, but in spite of continuing the aureomycin blisters began to appear again and he died ten days later (Whittle, 1950, *Lancet* (i), 139). Our patient had hæmorrhages into the blisters from the first and estimations showed complete absence of vitamin C in his plasma; he was in fact in a subclinical scorbutic condition. With vitamin C in large doses the hæmorrhagic character of the lesions cleared, but his condition appeared otherwise unaffected.

Dr. Brian Russell: I have recently treated a patient suffering from severe erythema multiforme (the Stevens-Johnson syndrome) with aureomycin. The temperature rose and the general condition deteriorated so that it was not considered justifiable to continue.

Dr. I. B. Sneddon: My colleague Dr. H. R. Vickers has recently tried aureomycin in a case of severe pemphigus vegetans involving the axillæ, arms and groins. A dosage of 1 gramme daily was used for four days. There was then no sign of improvement and treatment was discontinued.

Neurofibromatous Nævus.—A. MURRAY STUART, F.R.C.S.Ed.

W. F., aged 16.

History.—Occipital hæmatoma at birth, which subsided, leaving a discoloured patch. At the age of 4, growths appeared on the patch.

When first seen (11.7.40) he presented numerous hard tumours on the occiput and several pigmented nævi on the trunk.

He was treated by applications of thorium X and CO_2 snow.

Section of one of the occipital tumours on 2.9.40 showed: "Epidermis very thin and devoid of papillæ. Tumour is situated in the corium and consists of round and irregular cells arranged in alveoli. Many of the superficial cells show granules of melanin."

He was not seen again until 22.8.49. The lesions on the occiput had remained flattened and quiescent until three years previously when they had commenced to increase in size and number.

Present condition.—He now shows a mass of very hard tumours covering the occiput (Fig. 1). There are also numerous similar pin-head to pea-sized tumours on the chest, back and upper arms, and several pigmented moles in the same regions.



FIG. 1.—Neurofibromatous nævus.

Histology of tumours from scalp and flank (29.10.49): "Sections of each specimen show the structure of a pigmented mole with many nævus cells (mostly non-pigmented) arranged in nests, in columns and diffusely, lying in a rather dense collagenous stroma, covered by intact epidermis whose basal layer shows a variable amount of pigmentation and in places fraying and the development of intra-epidermal nævus cells (Fig. 2). In the deeper parts of the tumours there is a tendency to a whorled neurofibromatoid structure as well as some angioma-like multiplication of capillaries" (Fig. 3). W.R. negative. No relevant family history.

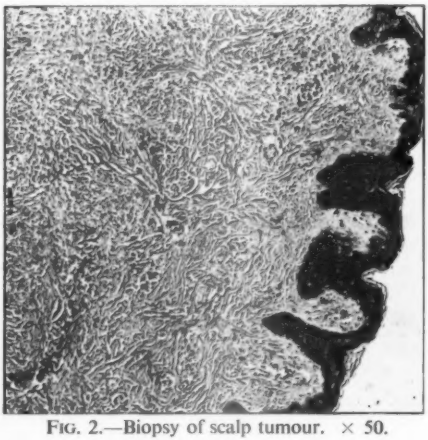


FIG. 2.—Biopsy of scalp tumour. × 50.

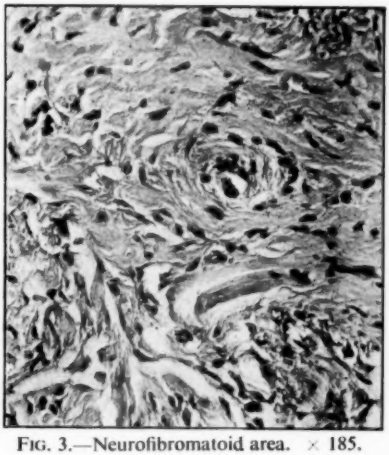


FIG. 3.—Neurofibromatoid area. × 185.

Comment.—The case described by Lipman Cohen (1945) appears to be very similar both clinically and histologically.

The history of this case is particularly interesting in that nævus cells and neurofibromatoid elements are present in both the scalp and trunk lesions.

Attention was first drawn by Soldan (1899) and later by Masson (1926) to the association of pigmented moles with local neurofibromatoid changes. Willis (1948) is of the opinion that these changes together with the angiomatous character of the capillaries are manifestations of disturbed development of all the ingredients of the skin.

My thanks are due to Dr. Cardew for the photograph and to Dr. Clay for the histology.

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Dr. E. Lipman Cohen: My patient, a man aged 34, had a very similar condition clinically and histologically, although it was milder. At birth and for a few years after the condition resembled a flat stain and it was not until early childhood that the tumour formation started. I called it a neurofibroma.

Dr. F. Parkes Weber: I take it that the condition of the scalp in this case may be roughly classed as a nævoid (not acromegalic or acromegaloid) type of cutis verticis gyrata ("bull-dog scalp" or "whirlpool scalp") though the scalp is nodular rather than gyrate, furrowed or striated. In very rare cases the microscopic appearance has suggested a neurofibromatous origin, as I think it does in the present case; but that does not signify that the patient actually has full-blown neurofibromatosis (Recklinghausen's disease). I think about one in two hundred persons have one or more nævoid lesions resembling neurofibromatosis, which never progress to full-blown neurofibromatosis.

This is my explanation of the case and I am exceedingly glad to have seen it, because it is the first case exactly of this type which I have ever seen.

Poikilodermia (Lane).—J. S. PEGUM, M.R.C.P. (for L. FORMAN, M.D.).

Mr. W. Engineer's inspector, aged 60.

History.—The patient has had a dry skin for very many years. The present condition began ten to fifteen years ago with darkening of the skin of the legs and has since spread upwards. Brown spots appeared on the hands in 1945. The brown patches on the trunk may have been present two years or longer.

The face and hands are less discoloured now than two years ago, when the patient gave up working with oil as a gun-barrel rifler, an occupation which he pursued for thirty years. The skin does not irritate much, but scales a great deal. There is no history of weakness or of swelling of the eyelids.

Previous diseases.—Mild eczema of the legs while a boy. Nervous breakdown at the age of 20.

On examination.—The skin is dry, scaly and shows fine wrinkling. On the sides of the chest and abdomen there are vertical, slightly depressed and pigmented streaks. On the abdomen there are three well-marked patches of discoloration, which show erythema, atrophy and pigmentation in a reticular pattern. Back: Over both scapulæ, posterior axillary folds and both iliac crests, there are areas of reticular erythema and pigmentation. Over the small of the back there are raised transverse linear lesions. These are palpable and resemble mildly hypertrophic scars. There is no history of injury in this region. Legs: There is a livid discoloration, and scaling and patches of erythema, atrophy and pigmentation on thighs and buttocks. The lower legs show ichthyotic scale, atrophy and pigmentation. There are areas of lichenification on both ankles. Arms: There are patches of poikiloderma on both arms. Mucosæ normal. On some of the discoloured patches there are small lichenoid papules.

Blood count within normal limits. Wassermann reaction negative.

Histology.—The corium shows an infiltrate with lymphocytes in upper third. There is œdema. The arrectores pili muscles show vacuolation and degeneration. The dermo-epidermal junction is flattened. There is œdema of the prickle and basal cells.

Treatment.—Course of calciferol. Course of testosterone injections. Neither had any effect on the skin lesions.

Dr. F. Parkes Weber: I am very interested in this case, as it shows transverse cutaneous striæ in the small of the back, which are rather of a "hypertrophic" than of an atrophic type. I believe that there is a "hypertrophic" or reactionary form of striæ atrophicæ in which the atrophic lines are filled up with sero-cellular or connective tissues, so that they are raised rather than depressed.

What I want to know is whether such transverse lines are recognized in poikilodermia or not. The patient has to bend a great deal in his work, the bending stretches the skin of the back longitudinally, which favours the local arrangement of the atrophic process into transverse lines. In cases of striæ atrophicæ of the back, if the lines are transverse, one is almost certain to find that either the patient has in some way been stretching the skin of his back or has been lying in bed with a bolster under his shoulders and upper back. Longitudinal stretching of the skin of the back helps to determine atrophic lines at right-angles to the length of the body.

Dr. Forman: As far as I know there is no peculiar liability for the skin to split in this way. I should have thought it was the Lane type of poikilodermia.

Sisters with Familial Benign Chronic Pemphigus (Gougerot, Hailey and Hailey).—H. HABER, M.D., and BRIAN RUSSELL, M.D.

I. Mrs. C. C., aged 32.

At the age of 27 first complained of an eruption on the right side of the neck. This recurred periodically in a mild form until July 1948 when she was three months' pregnant, and the condition became more extensive. The eruption starts as a red patch which forms blisters and then extends. The next attack occurred during lactation and the condition has improved since weaning the child in October 1949. She occasionally gets patches in the axillæ and groins and also cracks at the angles of the mouth. Friction from a dress or coat brings up a red patch.

On examination.—There are exuding, lightly crusted, erythematous patches with marginal epidermal detachment in axillæ, right more than left. Nikolski's sign positive over clavicle. A few pedunculated warts on neck and in axillæ.

II. Miss M. G., aged 30. Post-office clerk.

At the age of 21 developed a blistering eruption around the neck which persisted for three months. The condition has recurred periodically, sometimes also involving the popliteal and antecubital regions, under the breasts, and the groins. The rash starts as a redness of the skin which becomes blistered. One outbreak was followed by furunculosis. For family history, see Fig. 1.

Her health otherwise seems to be normal. Menstruation is regular.

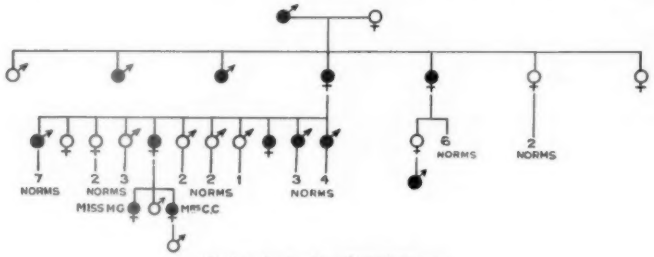
On examination.—There is profuse pityriasis simplex capitis and there has been pityriasis steatoides on the chest and back. On the sides of the neck and in the antecubital regions there are areas of erythema with blistering and denudation. There are a few pedunculated warts on the neck and in the axillæ. Nikolski's sign negative.

NOTE.—Attention is called to the Addendum *Proc. R. Soc. Med.* **43,** 398 in which Professor H. Gougerot refers to his description of this dermatosis in June 1933, nearly six years before the paper published by Hailey and Hailey.

Dr. Russell: The family tree shows inheritance for three and possibly four generations of skin troubles consisting of redness and blistering of the neck from chafing by clothing, and in some cases involvement also of the flexures.

The patient, M. G., shows marked evidence of the seborrhœic state in addition, which tends to mask the diagnosis.

The patient, C. C., emphasizes aggravation of the condition during pregnancy and lactation.



Black indicates the affected persons.

FIG. 1.

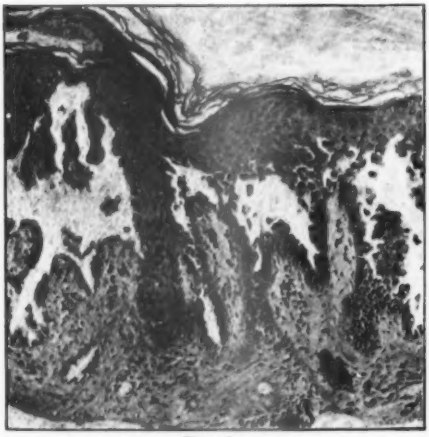


FIG. 2.

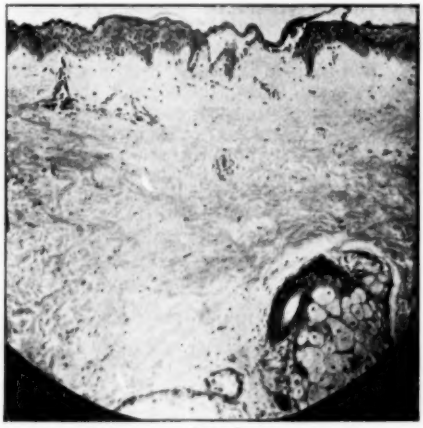


FIG. 3.

Familial Benign Chronic Pemphigus.

Dr. Haber demonstrated several sections of biopsies performed on both sisters.

The outstanding feature is the formation of clefts, fissures and bullæ within the epidermis, which usually exhibits acanthosis and irregular downgrowth of the rete pegs. Except for the stratum corneum, every layer of the epidermis may be affected. According to the severity of the affection, different degrees of epidermal disintegration may be encountered. Some lesions exhibit fine cracks only; others show deep clefts running through the epidermis in different directions. In such cases half of the epidermis may be torn off down to the middle layer of the stratum malpighii. Papillary projections covered by the germinal layer only may be found. If bullæ are formed, they too may be found in different layers containing pale staining fluid, a few red blood cells and groups or individual cells of the epidermis.

The epidermal cells themselves have undergone a characteristic change. They have become spherical, have lost their prickles and their protoplasma has become more homogenized, thus giving the cells a more rigid appearance. They can be seen lying individually or in clusters, but in some places they still stick together, giving the epidermis the appearance of a "dilapidated brick wall".

Within the corium there is mild or severe inflammation which is secondary to the epidermal changes. The occasional absence of the elastica in these regions is of no significance.

Fig. 2 illustrates a characteristic lesion. There is histologic evidence that the condition represents a generalized epidermal defect, and that the typical sites of predilection of the disease are due to friction, moisture or warmth.

In one of the patients, several lesions developed after the application of leucoplast to a clinically normal-looking skin of the trunk. Histology revealed the typical lesion of the condition. The other sister showed seborrhœic dermatitis. Biopsy of a small patch revealed fine cracks within the epidermis indicating that the trauma of biopsy only produced rupture of the intercellular bridges. With the

consent of both patients, normal-looking skin of the trunk was rubbed with a piece of gauze. In both cases erythema developed within a few seconds, followed in one sister by punctate petechiæ. Biopsy performed in both cases a few minutes after showed characteristic cracks within the epidermis, apparently due to friction. The conspicuous feature was that the epidermis cells still showed their prickles, indicating probably that the peculiar changes of the individual cell itself are secondary to the rupture of the intercellular bridges.

Fig. 3 shows a characteristic crack within the epidermis after the skin has been rubbed for a few seconds. There is a cleft running from the stratum corneum right down to the papillary body; the cells themselves still show their prickles. A few red blood cells within the artificial bulla explain the petechiæ appearing after the rubbing. Apparently the epidermis was torn right down the papillary body injuring a capillary which bled into the cleft.

It has also been observed that the epidermis of a normal-looking area will show evidence of degeneration by exhibiting peculiar vacuolation. It all indicates that we are dealing here with a generalized epidermal defect. Although there are no corps ronds demonstrable, the histology shows a close relationship with Darier's disease, which does not imply that the two diseases are identical.

Epidermolysis bullosa does not show any histologic resemblance to familial benign chronic pemphigus.

Dr. Alice Carleton: The mother and uncle of these two young women are patients of mine. The condition was clinically much easier to recognize in the mother than in the other patients. She had the appearance which has been described as "the tide receding from mud flats". Her patches cleared up and got worse in a most incomprehensible way, quite unconnected with any treatment. It has been suggested that this dermatosis is worse in hot weather. That has not been true of my two patients, who were actually better in the summer.

Erythema Multiforme Perstans (Erythema Elevatum Diutinum).—H. HABER, M.D., and BRIAN RUSSELL, M.D.

Mrs. E. W., housewife, aged 27.

History.—In January 1949 had treatment for a carbuncle with sulphonamides and penicillin. Shortly before this she first noticed painful swellings on the arms and legs, which have persisted ever since, varying only in intensity. The sites involved are the extensor surfaces of the limbs, the shoulders, buttocks (Figs. 1 and 2), and to a lesser extent the sides of the neck and very slightly on the body. The lesions itch, ache and throb.



FIG. 1.



FIG. 2.

Erythema Multiforme Perstans.

On examination.—Obese (since December 1948, but she is now losing weight). The eruption is polymorphic, consisting of nodules, in some places skin-coloured, in others pink or bluish-red. The nodules are dome-shaped with a few more extensive plaque-like infiltrations. On excitement or after friction, the lesions become more obvious and resemble wheals. There is a diffuse erythrocyanosis between the nodules. There is no true urtication. Retinal vessels normal. Blood pressure 120/70. Liver, spleen and lymph nodes are not enlarged.

Past history.—The patient has one child aged two years, and has had three miscarriages, the last eighteen months ago.

General health.—She suffers from recurrent bronchitis. She has recently been investigated for vaginal discharge which has been present since the menarche but has been worse since the miscarriage in August 1948. No organic cause was found: the vaginal swab showed a few monilia and many mixed organisms. Catamenia have always been irregular, 1–4 periods per annum, each of two days' duration.

Investigations.—Wassermann and Kahn reactions negative. X-ray of chest—no evidence of lung disease. Blood count within normal limits. Mantoux reaction: 1 : 10,000—faint erythema 1 cm. diameter; 1 : 1,000—erythema 4 × 2·5 cm.

Skin histology (10.10.49).—There is collagenous degeneration in and around the smaller arterioles and an infiltration of polymorphonuclear and eosinophil cells.

Treatment with antihistaminic drugs and vitamin E has proved ineffective.

Dr. Russell: I was asked to see this patient in a gynæcological ward for her persistent nodular yet urticaria-like eruption. Biopsy revealed degenerative periarteritis but the patient did not seem very ill and the E.S.R. was only slightly raised. There was moderate eosinophilia. The blood pressure was not raised and the urine was normal. The condition seems intermediate between urticaria and periarteritis nodosa malignum. Is it, in fact, a periarteritis nodosa confined to the dermis, an hypoergic reaction of abortive urticaria which, owing to failure of the normal response, has led to endothelial damage so severe that collagenous degeneration bordering on necrosis results?

The histological picture makes it clear why antihistaminic drugs are now ineffective, the process being irreversible.

History.—In 1894 Crocker and Williams described a persistent nodular eruption of the skin occurring chiefly in children. The type described by Crocker and Williams and also by Bury (1889) occurred in the young (5–30) with asymmetrical, local lesions over the joints and palms, and it is probable that this "Bury type" is a variant or later stage of some cases of granuloma annulare that do not involute spontaneously. Hutchinson described two remarkable cases of "symmetrical purple congestion of the skin in patches with induration occurring in gouty elderly men". These were probably the first cases described of the condition presented to-day.

Crocker and Williams confused the issue by including both the Bury type and the Hutchinson type in the one clinical title of Erythema Elevatum Diutinum.

Weidman and Besancon (1929) and Weidman (1948) regarded it as erythema multiforme of a persistent form from a rheumatic or toxic focus. They described the toxic hyalin degeneration of the reticular fibrillæ around the capillaries leading to a swollen collagenous appearance. The lesions in their patient ultimately regressed to areas of pigmentation.

Ketron (1944) described a patient observed for nine years, Coombes, Behrman and Saperstein (1948) described 2 cases and gave the diagnosed features as rough symmetry, persistence, nodules not discrete but raised and red, involving limbs, buttocks and neck (as in this patient). Weiss, Cooper and Gottschalk (1948) described 3 cases.

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Dr. Haber demonstrated a slide of the case (Fig. 3). The epidermis showed mild hyperkeratosis, acanthosis and attenuation of the epidermo-dermal junction. Within the corium there was a dense polymorphonuclear infiltrate surrounding the whole vascular network. The blood vessels showed in some places proliferation of the endothelial linings and the collagenous stroma of the infiltrate appeared to have undergone slight degeneration round a few vessels. There was no obliteration or thrombosis demonstrable. The collagen in between the infiltrate appeared to be normal and the inflammatory reaction round the blood vessels made a rather patchy appearance. The histological picture was striking and unique in skin pathology.

Weidman described two cases of erythema elevatum diutinum in which a polymorphic infiltrate round the blood vessels was a characteristic feature of the condition. In addition to this there was also a peculiar thickening of the perivascular reticulum fibres which stained deeply eosinophilic. Weidman labelled the



FIG. 3.—Erythema Multiforme Perstans.

change toxic hyaline and regarded it as pathognomonic, but in his opinion the absence of that change did not exclude erythema elevatum diutinum. He regarded the skin manifestation as an expression of bacteriæmia but admitted that any toxic damage might produce the same histological change.

Although there was no toxic hyaline demonstrable in this section it is possible that it represents an earlier stage in the development of the lesion and further biopsies at a later time could probably produce the characteristic change. On histological grounds, therefore, this case is to be regarded as erythema elevatum diutinum.

Macular Atrophy in Syphilis.—B. SCHWARTZ, M.B. (for H. W. GORDON, M.C., F.R.C.P.).

Mr. C., aged 57, was first seen in November 1949 in the V.D. clinic at St. George's Hospital during routine investigation of his pregnant wife's positive W.R. He has been married for two years.

Initially he gave no history of venereal or of skin disease, but later said that three years earlier, after intercourse with an unremembered woman, an ulcer developed on his penis. At the same time he had a rash on the back which started as "small white blisters which irritated for a short time".

On examination he was found to have: An annular syphilide near the left elbow. Papular plantar syphilides on both feet. The present lesions, viz. numerous round and oval, pinkish, soft swellings scattered in the lines of cleavage, chiefly on the back and also on the flanks and chest. The lesions vary in size from one-quarter to three-quarters of an inch, have a surface like crinkled tissue paper and are best viewed from an angle. On compression there appears to be loss of some of the underlying tissue (Fig. 1).

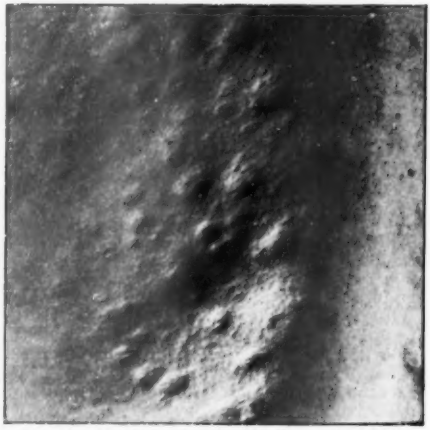


FIG. 1.—Photograph taken in November 1949.

Scarring of the glans penis, strongly suggestive of a previous primary chancre.

The Wassermann and Kahn tests were strongly positive.

Examination of the cardiovascular and central nervous systems showed no abnormality.

Anti-syphilitic treatment caused rapid disappearance of the lesions on the feet and arm but has had no effect on the atrophic lesions on the back.

Histological examination, November 1949 (Dr. H. Haber).—"The epidermis shows flattening of the epidermo-dermal junction in one place, but is otherwise apparently normal. Within the corium there is probably a tendency of the collagen to run parallel to the epidermis. The appendages are scanty. The elastica does not show gross changes."

Comment.—The case is presented as one of macular atrophy, an uncommon manifestation in syphilis. I can find no references to it in the English literature since Dr. Dowling described a somewhat similar case (1927). Dr. Dowling reported that there had been only 4 previous cases shown to this Society.

Since then two groups of cases have been described by American workers—a primary group where there has been no known preceding dermatosis, and a secondary group. The primary group includes the condition of "multiple benign tumour-like new growths of the skin" described by Schweninger and Buzzi (1891). The present case appears to be clinically indistinguishable from these.

Cases in the secondary group have been preceded by known dermatoses which include lupus erythematosus, leprosy and atrophic lichen planus. The majority of cases, however, occur in syphilis and have been described in all stages in that disease. The atrophy in syphilis may replace the lesions of the disease as a secondary sub-group, or may arise *de novo* as a primary sub-type. This case is probably rightly placed in the last group.

Histologically the lesions should show a loss, or partial loss, of elastic tissue. The sections in this case do not bear this out entirely, possibly because we biopsied a lesion which was not very atrophic. However, in cases reported before Dr. Dowling's paper, it was seen that the loss of elastic tissue was rather a late phenomenon and we hope to complete the present case with further sections.

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Dr. C. H. Whittle: The lesions remind me of those in a case we showed here of epidermolysis bullosa with the albo-papuloid dystrophy of Pasini (1948, *Proc. R. Soc. Med.*, **41**, 762). These particular lesions did not give on palpation the curious impression of a hole in the skin. I was wondering if the speaker had gone into the question of any family history of dystrophic conditions preceding this case.

Dr. Schwartz, in reply to Dr. Whittle: The family medical history was gone into during the routine investigation of the case and, as far as could be ascertained, there were no relevant skin diseases or dystrophic conditions.

Exfoliative Erythrodermia with Lymphadenopathy.—S. P. HALL-SMITH, M.R.C.P.Ed. (for W. J. O'DONOVAN, O.B.E., M.D.).

S. M., aged 34, cabinet maker.

History.—Three-and-a-half years ago, blisters appeared between fingers; working at that time with synthetic glue. Later weeping red patches appeared. Treated for scabies with benzyl benzoate which he believes initiated the present trouble; within one week of treatment the rash had become generalized with severe irritation.

Diagnosis in April 1946 was extensive seborrhœic dermatitis affecting particularly the extremities.

August 1946: Admitted Middlesex Hospital under Dr. Ray Bettley. Sections showed appearance of seborrhœic dermatitis. Blood count and chest X-ray showed no abnormality. Response to treatment was extremely slow.

February 1947: Bilateral intranasal antrostomy was performed for chronic sinusitis, but caused little improvement.

May 1947: Superficial X-ray therapy was instituted and continued over a period of two months to most of the body surface, dosage varying from 275 r to 500 r.

Slow improvement until May 1948 when he was discharged from the Middlesex Hospital. Remained an out-patient until May 1949 when he attended the London Hospital Out-Patients. Received various symptomatic treatments there until admission in November 1949. Rash has remained generalized and much the same during whole of this period, although it has improved with further X-ray therapy. General health good.

Past history.—No illness apart from usual exanthemata as a child. No history of past skin trouble, urticaria, hay fever, asthma or other allergic disease.

Family history.—Father killed in World War I, mother alive and well. Three brothers, wife, one child aged 16, all alive and well. Both parents were of Russian Jewish stock.

On examination.—Skin: Generalized erythrodermia, confluent over most of body surface, with the exception of face and dorsa of hands and feet, which show some interspersed areas of normal skin. The erythrodermic areas are lichenified and exhibit a pleomorphic and confluent papular appearance. The skin of penis and scrotum is normal. The whole area shows mild exfoliation. Palms normal. Soles show scattered pink infiltration areas with scaling.

Lymph glands: Generalized enlargement. Large rubbery glands palpable in both groins. Glands in axillæ and neck are smaller though easily palpable.

Other systems normal.

Investigations.—5.5.49: R.B.C. 4,900,000; Hb 85%; W.B.C. 12,900 (P. 42%, E. 34%, L. 19%, M. 5%).

5.11.49: Hb 97%; W.B.C. 8,100 (P. 36%, E. 39%, L. 23%, M. 1%).

5.11.49: E.S.R. (Wintrobe) 28 mm. in 1 hour. W.R. negative. Total plasma proteins 5·4 grammes per 100 c.c. Mantoux test positive 1 : 1,000. Chest X-ray: Lung fields clear.

18.11.49: *Sternal puncture*: Within normal limits though eosinophilia confirmed.

28.11.49: Biopsy of lymph gland from inguinal region: Severe acute and chronic inflammation with some areas where the histiocyte proliferation is found not only in the sinuses but in the medulla; in these there are some atypical nuclei. Slight focal deposition of melanin pigment.

10.1.50: W.B.C. 10,200 (P. 39%, E. 27%, L. 26%, M. 6%).

This is not ordinary chronic inflammation, and, although at present it is not typical of any reticulosis, it may develop into one.

Skin of right thigh—slight diffuse acute inflammation of hyperplastic epithelium. Severe inflammation of subepithelial tissue with collections of eosinophil leucocytes and scattered Russell bodies.

Comment.—Clinically and histologically this case appears to agree with a series of 13 cases discussed by Robb-Smith at the Annual Meeting of the British Association of Dermatologists in 1942; he used the term Exfoliative Erythrodermia with Generalized Lymph Node Enlargement to describe these cases.

Groups of similar cases have been described by Sulzberger and Garbe (1937) under the title of Exudative Discoid and Lichenoid Chronic Dermatitis, and Cannon (1939) describes a series of cases which he called Allergic Dermatitis simulating Lymphoblastoma. The latter observer in a series of 8 cases was able to incriminate an external irritant cause; it is interesting to note that our patient thinks his trouble was initiated by painting with benzyl benzoate, and that he also worked in a dusty atmosphere as a cabinet maker and used various synthetic glues.

All but one of the 17 cases described in the above two series were of Jewish stock, as is our patient. A paper by Coombes and Bluefarb (1941) entitled Giant Follicular Lymphadenopathy appears to deal with the same condition.

In brief these cases should be differentiated from the premycotic eruptions and the leukotic erythrodermias, and it is important to stress that it is only by following up a sufficient number of these cases that one can acquire information about their prognosis and response to treatment.

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Multiple Epitheliomata.—ALLAN YORKE, M.R.C.S., L.R.C.P.

Mr. T., aged 50, bank clerk. Lived in Brazil from 1921 to 1924. Taken "tonics" occasionally.

1918: Accident with laceration at left supra-orbital ridge and fractured right tibia and fibula.

History of present condition.—Multiple nævi of face, neck and trunk as long as he can remember.

1934: First lesion at bridge of nose "which would not heal".

1936: Branchial cyst. Removed by Mr. Norman Lake.

1937: Saw Dr. A. C. Roxburgh at St. Bartholomew's Hospital who diagnosed a rodent ulcer; this was treated by excision and X-radiation.

There was a recurrence six months later and radium, advised by Mr. Norman Lake, proved unsuccessful, as did X-radiation subsequently employed at the Royal Salop Hospital.

This exacerbation at the nose heralded the onset of the lesion at the sacrum.

1941: Sir Archibald McIndoe saw him at the Queen Victoria Hospital, East Grinstead. In a personal communication he writes: "When I examined him I found he had a recurrent rodent ulcer on the bridge of the nose together with one on the back. I removed both and reconstructed his nose with a forehead flap, as I feared a further recurrence. The pathological report showed that it was a typical basal-celled carcinoma."

Insidiously he had developed further lesions at the right eyelid, left ear, right and left cheeks—and states the lesions are still appearing on the face and trunk.

On examination.—There are multiple flat and raised, pigmented and non-pigmented nævi of the face, neck and trunk. The left eyebrow and infra-orbital regions together with the right retro-auricular region and scalp above the right temple show multiple rodent ulcers ranging from crusted firm elevations to one about half an inch in diameter. Multiple superficial basal-celled epitheliomata of varying shape and size roughly aligned at the paravertebral region and presternal area.

Comments.—It seems unlikely that the lesions on the exposed parts can be described as a solar reaction on the one hand and those on the non-exposed to arsenic ingestion on the other.

This patient had a branchial cyst removed in 1936. He has widespread nævi; the lesions are not responsive to X-radiation or radium, and are constantly appearing. It is suggested that they may be of nævoid origin.

The following cases were also shown:

Sarcoidosis.—Dr. THERESA KINDLER.

Basal-Cell Carcinoma of the Palm.—Dr. ARTHUR ROOK.

(These cases may be published later in the *British Journal of Dermatology*.)

Section of the History of Medicine

President—E. Ashworth Underwood, M.A., M.D., D.P.H.

[*January* 4, 1950]

Infant Feeding-Bottles in Prehistoric Times

By A. D. Lacaille

(*The Wellcome Historical Medical Museum*)

Since the beginning of this century our knowledge of the history of pædiatrics has been considerably increased by references to vessels used in remote antiquity in the artificial feeding of infants. Perusal of the literature on the subject shows that inquirers, who have dealt more particularly with archæological aspects, have made much of Roman glass and pottery examples as the forerunners of the modern feeding-bottle. So recently as 1947 F. Tubbs reaffirms this opinion [1].

Such bottles came to be commonly made and employed where the Romans imposed their civilization. Specimens have been found in Britain, France and Germany. The fact that so many authenticated items have been recovered from the graves of infants leaves no room for speculation on their purpose. Examples have been cited by H. Syer Cuming in 1870 [2]. He correctly interpreted them, though some of his predecessors in archæological inquiry did not. However, that careful antiquary, the Abbé J.-B.-D. Cochet, mentions several [3], attributing some, by reason of the relics associated with them, to Gallo-Roman times, that is to say between the arrival of Cæsar and the fifth century of this era.

Some of the small vessels cited by Cochet held the traces of wine or honey, and, he thought, milk also. More precise, however, was the result of the analytical test of a white deposit in one of two small vessels, Fig. 1, believed to be Romano-German, from Sir James Young



Fig. 1.—Feeding-bottle ; believed Romano-German. (After J. A. Smith.)

Simpson's collection, presented by his son to the Society of Antiquaries of Scotland in 1871 [4]. Identified by this test as casein, the residual matter showed beyond question that the vessel was, in fact, an infant's feeding-bottle.

Certain authors have claimed that the prototypes of these and the ancestral Roman examples lie in Greek vases going back to between 700 and 500 B.C. This, however, is to ignore evidence from the sites of pre-literate societies, and even of communities in stages of

prehistoric cultural development, for the origin of the feeding-vessel. That artificial feeding was practised centuries before the impact of Roman civilization was felt in Gaul appears from characteristic vessels attributed by Joseph Déchelette [5] to the late Bronze Age (IV), or very early Iron Age (Hallstattian), about 900 B.C., that is to say when the winged palstave, or narrow axe, of bronze was giving place to the socketed form. They are reported from land-stations and from the sites of lake-dwellings. Moulded in typical, fine handmade ware, the examples, Fig. 2, Nos. 1 and 2, are from Nierstein in Rhenish Hesse, 5 and 6 respectively

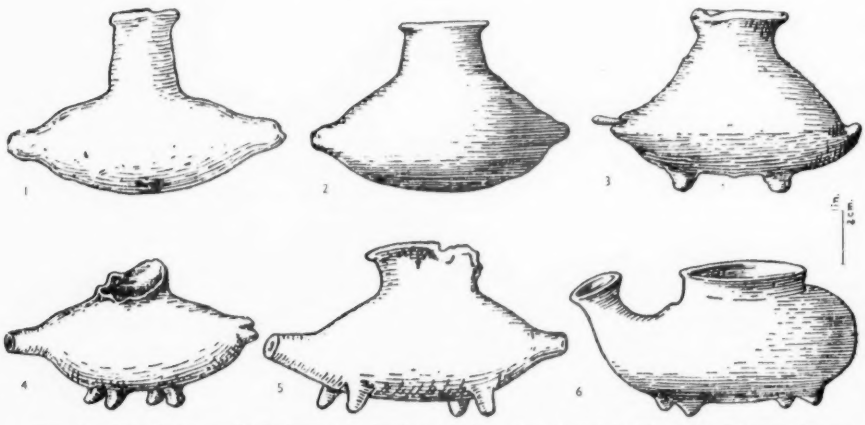


FIG. 2.—Late Bronze—Early Iron Age feeding-bottles: Nos. 1 and 2, Nierstein, Rhenish Hesse; Nos. 3 and 4, Grésine, Lac du Bourget, Savoie; No. 5, Tulln, Lower Austria; No. 6, Platenic, Bohemia. (After Déchelette.)

from Tulln, Lower Austria and Platenic, Bohemia, and Nos. 3 and 4 from Grésine on the Lac du Bourget (Savoie), in south-eastern France.

It is evident that these six specimens, from 12 to 15 cm. long, belong to the same culture complex. All are of ovoid shape, and have the common feature of a central and wide cylindrical neck for filling. Each is provided with a spout, nipple-shaped in Nos. 1, 2 and 3, plain and tapering slightly in Nos. 4 and 5. No doubt for the sake of symmetry, a similar but imperforate projection has been made opposite the effective tube. The bodies of Nos. 1 and 2 are plain, but in Nos. 3, 4 and 5 they are furnished with four small feet to lend stability to the vessel. In No. 6, footed likewise, the upcurved extension widens to 2·5 cm. at the everted rim. Whereas it is obvious from their ends that Nos. 1 to 5 must have served for infants, it appears from its relatively wide-lipped spout that No. 6 was intended not for a suckling's use, but rather for an adult's. The last may therefore be regarded as a fore-runner of the modern feeding-cup of the sick-room. So far as known, it stands as the oldest European example on record.

It is strange to reflect that modes of artificial feeding should have obtained in Europe among peoples whose culture was incomparably inferior to that of the Egyptians of the later dynasties, yet earlier in time than the European. Still, it is well known that in ancient Egypt the royal nurses were important persons. But dynastic Egypt has bequeathed no material or pictorial memorials of artificial feeding, though S. H. Sadler figures [6] a symbolic scene, representing the Queen Hatshepsut being fed by Hathor as a sacred cow from Thebes in the Temple of Deir el Bahri, dated to about 1500 B.C.

While, then, the highly civilized Lower Nile so far affords no evidence of the use of aids to feeding the very young or sick, the prehistoric site of Jebel Moya, between the Blue and White Niles, over 1,200 miles from the Mediterranean Sea and 160 miles south of where Khartoum stands to-day, furnishes proof that children of tender age were the object of considerable care where the rate of infant mortality seems to have been high. This station, the Mountain of Water, rising out of the mimosa scrub, was intensively explored by the late Sir Henry Wellcome during the four seasons preceding the war of 1914–18. His excavations yielded the remains of occupation ranging over a period from about 1000 to 400 B.C. While this is so much later than much of the best of Dynastic remains, yet Jebel Moya was a backwater and the resort of a community whose culture was essentially Neolithic. The occupants were the recipients of old cultural strains unaffected by advanced

ideas, save perhaps those of a well-developed potter's craft. This, like the other elements making up the industrial complex of Jebel Moya, seems to have come from different points in the west, whence it may be that women were forcibly removed to be wives or slaves. At Jebel Moya they would naturally continue to make the same kinds of ware and pots as they had done in their original homes.

The pottery produced at Jebel Moya is varied. It includes spouted vessels, some having been recovered from graves, whereof 13% are those of children. One of these deposits, Fig. 3, contained the bones of twin babes, thought to have been buried beneath a hut referable to the latest period of occupation [7]. Besides the children's remains there lay a pathetic nursery equipment consisting of two elegant spouted feeding-cups and a plain bowl. All three vessels, Fig. 4, are closely matched in size, averaging 3 cm. in height and 6 cm. in diameter, and made in fine, dark grey and buff ware.

For the nearest parallel to these small spouted feeding-cups we have to turn to the continent of Europe. In France, at Tours-sur-Marne (Marne) [8], a suckling's grave of the late Neolithic period, say 2000–1500 B.C., has yielded an example, 4·4 cm. high and flat-based, of typical coarse ware, Fig. 5. Of course it is impossible to link this relic chronologically or



FIG. 3.—Grave of twin babes, with feeding-vessels, at Jebel Moya prehistoric station, Anglo-Egyptian Sudan. (By permission of the Trustees of the late Sir Henry Wellcome.)

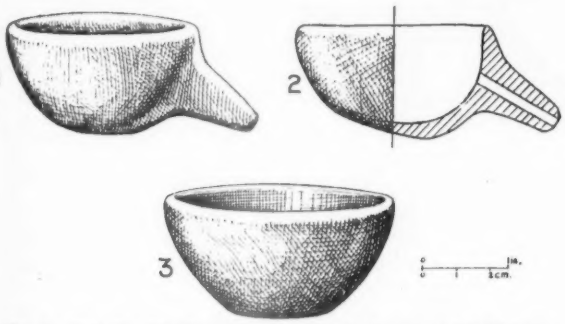


FIG. 4.—Details of feeding-vessels from twins' grave at Jebel Moya. (By permission of the Trustees of the late Sir Henry Wellcome.)

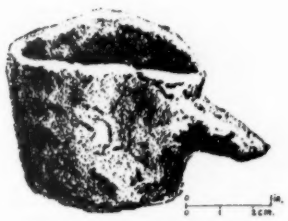


FIG. 5.—Feeding-vessel from an infant's grave; of Late Neolithic Age; Tours-sur-Marne (Marne), France. (After Goury.)

culturally with the remains from Jebel Moya. Nevertheless, the French specimen demonstrates that the use of artificial aids in the nursing of infants goes back to far higher antiquity, and to a culture less advanced than any mentioned in the foregoing. Now, pottery-making and cattle-raising were among the chief new activities introduced by the Neolithic people whose revolutionary *food-producing* economy replaced the *food-collecting* habits of the Old Stone Age. It may be permitted to surmise, therefore, that the fictile spouted feeding-vessel, mainly as a container for milk, was devised even earlier than is illustrated at Tours-sur-Marne, that it was in fact manufactured in western Europe from the inception of pottery-making and the rearing of stock animals, that is in the early Neolithic period, say between 3000 and 2500 B.C.

Having dealt with purely archæological aspects, we could, if space permitted, expand upon such points as typology and distribution, and also examine several problems suggested by this brief study. These would involve: (*a*) An inquiry based on historic analogy into the possible use of a ruminant's horn instead of, or as a precursor of, the pottery feeding-vessel; (*b*) a consideration of such means as a cow's or calf's udder to sheathe the pottery spout, contact with which in an unprotected state would assuredly injure the delicate mouth of a young child; (*c*) questions connected with sociology and population, why, for instance, certain exponents of prehistoric culture should have been at pains to preserve the life of infants; (*d*) the religious side indicated by the placing of feeding-vessels in the graves of babes, perhaps for use in an after-life.

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Ancient Egypt and the Origin of Anatomical Science

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ANATOMY as a science came to birth in Ancient Egypt. Though sired by the Alexandrian Greek fathers of anatomy, Egypt was its womb. The brilliancy of Greek scientific enquiry in the later centuries of the pre-Christian era achieved nothing, so far as anatomy is concerned, in its native land: for at home that enquiry lacked the opportunity and material for its legitimate exercise and was thus compelled to seek the one possible theatre of operation, Egypt. And hence Egypt, with her immemorial, unchanging culture, stands behind anatomical science (as behind so much else), if not strictly as mother, at least as foster-mother. For Egypt, accidentally, but none the less effectively, made possible the origin of scientific anatomy. She provided the materials, the opportunities and the necessary philosophical atmosphere essential to the questing Greek mind : indeed, but for the fortuitous circumstance that the Egyptians held uniquely distinctive beliefs concerning existence beyond the grave and that they gave concrete expression to those beliefs in the mummification of their dead, the beginnings of anatomical science would not have been made (or so adequately) when they were.

The precursor of the anatomist is the Egyptian embalmer. Alone among the peoples of antiquity the Egyptians, for religious motives, submitted their dead to extensive and elaborate techniques designed to preserve permanently the frame and lineaments of the deceased and which necessitated a manipulation of the cadaver unparalleled in intimacy elsewhere in time or place, productive incidentally of at least a quasi-scientific knowledge of human structure.

It would be erroneous, in the light of present knowledge, to regard the Egyptian embalmer as an anatomist or indeed as a scientist of any kind. He was a sacerdotal technician concerned solely with preventing the dissolution of the cadaver. His procedures were purely ritual in origin and intention and his techniques were strictly utilitarian in purpose. That anatomical knowledge resulted therefrom was accidental. Nevertheless such fortuitous knowledge was of the greatest importance, for it was unrivalled elsewhere in the world. It was the most extensive and the most detailed corpus of ascertained anatomical data extant, one denied to peoples who merely inhumed or cremated their dead. It certainly led to some speculation as to physiological function and, imperfect as it was, it formed a basis upon which, in due time, a truly scientific understanding could be erected.

It is worth considering how this Egyptian knowledge of anatomy was acquired. Mummification, coincident with the advent of the dynastic period, continued into the early Christian era, though generally in debased fashion in the later (Persian, Ptolemaic and Roman) historic periods. Its precise techniques, which varied from time to time, may be ignored here. But for three and a half millennia the human cadaver was explored internally with a degree of thoroughness otherwise unknown, and to the embalmer's hands and eyes was revealed infinitely more of human structure and topography than could be learned from the mere accidents of civil life or the wounds and injuries of war. Typically through a limited (90–110 mm.) flank incision the body cavity was completely cleared of its contents: the abdominal viscera, their vessels and even the peritoneum, were all stripped away together with the pelvic organs and their adnexa. The diaphragm was either removed entire or each cupola was cut through; the lungs, œsophagus and other thoracic structures were then detached, the heart and aortic arch alone being canonically left in situ: the trachea and adjacent structures were cut across at the root of the neck and removed likewise. After Dyn. XVIII the brain (previously ignored) was approached by a break made in the nasal fossa roof (ethmoid, more rarely sphenoid) and cunningly removed piecemeal, without injury to the falx and tentorium. (The tongue and eyes, like the heart, were left in position.) The very accomplishment of such procedures bespeaks an extremely accurate awareness of the precise topography, mutual relations and attachments of the main body organs.

The removed body-contents underwent further inspection, sorting and manipulation. For certain organs (stomach, lungs, liver, small intestine) had to be mummified separately for restoration (in one way or another) to the completed mummy. This business alone necessitated an anatomical nomenclature (the earliest known to medical history), and brought the shape, size, appearance, texture and consistency of the several soft parts directly to the notice of the embalmers. Inevitably they were habituated to a wealth of gross anatomical knowledge otherwise unavailable, and though their anatomical terminology may have been essentially that of the butcher, nevertheless it was something unique and historically valuable. Egypt could boast an acquaintance with the economy of the human frame without equal elsewhere : a prime, if unintentional, step had been taken along the unending road of anatomical science.

The embalmers, an honourable, traditional and priestly caste, transmitted their anatomical knowledge orally or gleaned it personally by apprenticeship to their craft. Despite their magnificent technical innovations and achievements, the Ancient Egyptians were devoid of interest in pure science : consequently no strictly anatomical papyrus is known. But some of their anatomical vocabulary may be gathered from the lists of body parts which occur as follows :

On the walls of the Saqqara pyramids (*Pyr. Texts*, 135 ; 148-9 ; 1303–1315), on Middle Kingdom coffins (*Coffin of Amamu*, XXIV, 11–18 ; P. Lacau, *Textes Religieuses*, XXVII), on the walls of Theban royal tombs (*see* E. Naville, *Litanie au Soleil*, pls. 14, 20, 21, 32), in the *Book of the Dead* (42; 172), *Book of Breathings*, and other funerary compositions, in the New Kingdom magical papyri (*Pap. Berlin*, 3027, 3, 6–5, 2; verso 4, 8–5, 5; *Pap. Turin*, 125, 5–11; *Pap. Leiden*, 348, verso 5, 1–6, 2; *Pap. Chester-Beatty*, VII, verso 2, 5–5, 6; *Pap. Ch. Beatty*, VIII, 7, 1–9, 6; *Pap. Vatican*, 36, on the 30th dynasty *Metternichstele*, II, 15–32), in the *Tanis Sign Papyrus*, 7, 11–10, 6, on various ostraca, and elsewhere.

Some hundred odd anatomical terms are thus known, the majority referring to the external parts and features. Some of the terms for internal parts or organs still await precise identification : others are more or less collective terms (e.g. *mtnu* for nerves, vessels, ligaments indiscriminately : *smu* for the " pluck "). Specific names obtain for heart, lung, kidney, bladder, stomach, bowel, uterus, vagina, diaphragm, spinal cord, brain, cerebral convolutions, and meninges. It is significant that the Egyptians wrote these terms with animal determinatives, thus manifesting their recognition of the homology between human and animal organs and incidentally proclaiming themselves the earliest comparative anatomists.

It would seem that the corpus of anatomical information resulting from the manipulative procedures of the embalmers facilitated some conception of physiological activity. There was a crude understanding of the heart's action and of the pulse and an appreciation of the continuity of the heart with " the vessels". The heart indeed (never the brain, which was treated as waste) was the imagined seat of the intelligence and personality : this organ was carefully preserved in situ and heart scarabs and funerary spells were employed to ensure its continued well-being, for loss or destruction of the heart meant annihilation in the Other World. Something too was known of the simple physiology of the intestinal canal, of the bladder and of the uterus, matters however not requiring much more than the exercise of ordinary post-mortem observation.

As already noted, anatomical study was neither the object nor the interest of the embalmer. Certain organs he had to preserve for ritual reasons and therefore to recognize and retain : others (e.g. spleen, pancreas, colon, trachea, œsophagus, genito-urinary) he discarded.

His anatomical terminology therefore for this latter class of structure necessarily remained minimal, generalized and " unscientific," much akin, in range and precision, to the butcher's nomenclature in matters veterinarian. And invaluable as was the age-old practice of mummification in compelling the constant inspection, preparation and manipulation of the human internal parts and organs and in thus establishing the earliest organized corpus of anatomical knowledge it nevertheless by its very nature precluded any strictly scientific exploration of the human frame. Dissection in the strict sense there was, and could be, none. Mummification aimed at the preservation of the body in its entirety and though this aim necessitated the skilful removal of the putrescible viscera and the specific treatment of the eviscerated trunk, it excluded from detailed observation whole areas and systems of the body. It afforded no opportunity for the investigation of, for instance, the neural, muscular and vascular systems. Even endowing the Ancient Egyptian with a passion for abstract knowledge of anatomy for its own sake (something wholly alien to his temperament) the embalmer's workshop afforded but limited facilities for the play thereof.

Extravagant claims therefore should not be made regarding the extent of Ancient Egyptian anatomical knowledge, and difficult or corrupt anatomical passages in the medical and magical papyri should be interpreted with caution. And there is so far no substantial evidence from the records of any inherent scientific interest by the Egyptians in any branch of natural knowledge.

What, then, is Egypt's claim on the attention of the anatomical historian ? This, that she, and she alone, made possible the beginnings of a scientific study of human structure at the hands of the Alexandrian Greeks.

Hippocrates (*c.* 400 B.C.) had given a somewhat confused account of the vascular system which may well have been derived from an Egyptian source (cf. *Pap. Ebers*, 99, 1–103, 18: *Pap. Berlin*, 13, 1–17, 1), and Diocles (350 B.C.) who had written " On the heart," describing the cardiac valves, atria and columnæ carnæ, may also have been indebted to Egyptian sources. But with the Alexandrians (300 B.C.–A.D. 150) the positive evidence is irrefutable. Herophilus of Chalcedon (*c.* 300 B.C.), Erasistratus of Chios (*c.* 290 B.C.), Rufus of Ephesus (A.D. 50), Soranus of Ephesus (A.D. 100), Marinus of Tyre (*c.* A.D. 100) and lastly Galen of Pergamum (A.D. 150–200) all conducted their anatomical researches in Egypt itself, even though Soranus and Galen worked later in Rome. In Ptolemaic and Roman Egypt, Alexandria was the cultural centre and the repository of traditional native lore. It was likewise the populous home of the wealthy, who still maintained (whatever their precise religious beliefs) the time-honoured custom of mummifying the dead. Hence the Alexandrian anatomists had the opportunity, denied them in their native homes or elsewhere, of making personal acquaintance with the internal mechanism of the human body, of association with the hereditary guild or caste of embalmers and of thus becoming possessed of the then greatest extant corpus of anatomical knowledge. Moreover, and doubly fortunate from the viewpoint of anatomical history, these last centuries of the pre-Christian era were, in Egypt, a period of debasement and degeneration in native practice. Mummification, though still traditional, was no longer the formal expression of profound religious convictions : no longer was the embalmer's prime concern the lifelike preservation of the cadaver as an essential to the deceased's spiritual welfare in another state of being. Less and less attention was paid to the essentials of preservation and more to the ceremonial accompaniments—the wrappings, the amulets and the coffin. This then is the period characterized by gaudy cartonnage coffins containing, very often, but ill-made mummies. Many such mummies are little more than eviscerated, resin-coated cadavera, the outcome of the most perfunctory work and in striking contrast to the excellent mummies of earlier periods. There is plain evidence, from the specimens themselves, that the body was frequently in bad state before its embalming began or that it fell to pieces during the process and was assembled for wrapping in singularly careless fashion. For insects and their larvæ have been found embedded in the resin used ; limb bones have been noted upside down or associated with the wrong side or even member; and the broken-off head has been discovered reaffixed to its trunk by bandages. Although well-made mummies of this late period do obtain, it is all too obvious that in general the old ritual art and craft of the embalmer was being lost or abandoned.

But this very deterioration in the practice and technique of mummification gave even greater scope to the Alexandrian anatomists. Access was now possible to regions and systems of the body unassailable in former days. The older religious scruples had disappeared and in a country where, for thirty-five centuries, there had been a unique absence of prejudice against manipulative violation of the cadaver, it was doubtless not difficult to carry anatomical exploration much further than that cursory examination of parts and organs permitted (indeed necessitated) by former traditional practice. And from their recorded observations it would appear that the Alexandrians did in fact avail themselves of the unrivalled opportunities thus open to them.

Whether or no Herophilus performed actual dissection (as Galen believed) he distinguished the arteries from the veins, described the meninges, the fourth ventricle and the torcular Herophili, gave the earliest account of the lacteals and named the prostate and duodenum. He placed the seat of intelligence in the brain.

Erasistratus described the cerebral ventricular system and traced the cranial nerves into the brain: he settled the origin of the great venous and arterial cardiac vessels, named the tricuspid valve and postulated a capillary system. Besides work on the lacteals he wrote accurately upon the trachea, the chordæ tendineæ, the atria and the endocardial valves. His mere record of achievements implies a familiarity with human structure which could derive only from dissection.

Rufus of Ephesus described the lens of the eyeball and was author of the first scientific anatomical nomenclature : Soranus described the pregnant uterus and Marinus was the author of several anatomical treatises.

By Galen's day Egypt was a Roman province and its customs had further changed. Presumably Alexandria no longer offered the anatomical facilities available four centuries earlier, for Galen worked there without ever dissecting the human body.

But in Herophilus, Erasistratus and Rufus scientific anatomy had its beginning, and Egypt made their pioneer labours possible: for nowhere else in the world was such unprejudiced and intimate exploration of the human frame feasible, nowhere else were men already so well acquainted with human visceral anatomy, and nowhere else existed any comparable corpus of purely anatomical knowledge. Anatomy as a scientific discipline came to life in Alexandria, the fruit of the Greek seed in the womb of Egypt.

[*February* 1, 1950]

Humphry Davy's Contribution to Anæsthesia

By F. F. CARTWRIGHT, F.F.A. R.C.S., D.A.

THE purpose of this paper is three-fold; firstly, to give some account of Davy's work on nitrous oxide and to endeavour to trace the chain of events which connects Davy with the introduction of anæsthesia; secondly, to correct a number of mistaken ideas about his early life and work; and, thirdly, to draw attention to the fact that, in this year 1950, we celebrate the one hundred and fiftieth anniversary of the publication of Davy's researches upon nitrous oxide; indeed, my purpose is to show that we are celebrating not merely this work alone, but the true "discovery" of anæsthesia.

Humphry Davy was born at Penzance on December 17, 1778, the first born of the five children of Robert Davy. For some two hundred years the Davys had been yeomen, farming the copyhold of Varfell in the parish of Ludgvan on the shores of Mount's Bay. Robert Davy was a younger son, but his elder brothers predeceased him and in 1784 he succeeded to the family property. Not only did he inherit the farm but also a considerable sum of money, for his father had been a builder with a large business; it was upon this account that Robert Davy had, in his youth, been apprenticed to a wood carver.

When the Davys left Penzance for Ludgvan, 6-year-old Humphry was left behind under the guardianship of John Tonkin, a surgeon, who had been guardian to Davy's mother. The boy seems in some measure to have been adopted by the old man, for one of Tonkin's account books for the period 1784 to 1795 contains particulars of his expenditure on Humphry; it is headed "This is not meant or intended as a charge against Mr. Davy, only for my own satisfaction to know what Humphry has from me from time to time, and what I have from them."

The greater part of Davy's schooldays was spent under the headmastership of a Mr. Coryton, a thoroughly bad type of master who seems to have made no attempt at teaching or discipline. Davy's education was hopelessly neglected; in after-years he declared that this had proved to be to his advantage, for he had learned, not from books, but from nature and from observation.

In 1794 Robert Davy died; he was an ingenious but shiftless man who had wasted much money in experimental farming and the dangerous speculation of improved tin-mining. In consequence, his family was left badly off; not in absolute necessity, for Mrs. Davy never had an income of less than £150 a year, which was certainly not poverty at the end of the eighteenth century; but sufficiently poor to make it impossible for Humphry to

continue his schooling or to go on to college. So in 1794, at the age of 16, he was apprenticed to John Bingham Borlase, grand-nephew of the great William Borlase who had been rector of Ludgvan some thirty years before.

Humphry Davy was a dreamy lad, living largely in a world of his own, absorbed in the beauties of natural history and of the Cornish landscape, beauty which he endeavoured to translate into verse. He was no mere versifier; his poems were of sufficient merit to attract the attention of and to be published by Robert Southey; in later years Coleridge said of Davy that, had he not been the first chemist, he would have been the first poet of his age. Davy was one of those rare mortals who, from early youth, have an absolute conviction that they are born to achieve greatness. He allows us to catch a glimpse of this sure belief in his notebooks for the year 1797; and at the same time he recognized that his defective education was a bar to his progress and he set about remedying the matter. We can still read, written down for us in his own hand, the exacting syllabus that he outlined for himself in 1797, a scheme of self-education covering philosophy, languages, the sciences, religion and many other subjects.

In the winter of 1797–8, in pursuance of his scheme, he embarked upon the study of experimental chemistry with such assistance as he could obtain from Nicholson's *Dictionary* and Lavoisier's *Elements of Chemistry*. His ingenious mind fastened upon Lavoisier's theory of oxidation; considering that Lavoisier had neglected to fit the phenomenon of light into his theory, Davy produced that work which formed the subject of his first publication; a fantastic theory which aimed to show that light is ponderable matter, capable of combination with other substances, particularly oxygen.

In that same winter of 1797 Davy made two friendships which were destined to alter the course of his life. Gregory Watt, the consumptive son of the great engineer, had been sent to winter at Penzance on the advice of his physician, Thomas Beddoes. Watt boarded with Davy's mother; he seems at first to have been repelled by young Humphry, but the two soon became fast friends; it was Watt, himself no mean scientist, who sent Davy's theory of light to Beddoes. The other lifelong friendship that he made in this winter was with Davies Giddy, who was destined to follow Davy in the Chair of the Royal Society. By a curious coincidence, Giddy was also connected with Beddoes, for he had been Beddoes' favourite pupil at Oxford; it was natural for Giddy to have copies of Beddoes' publications in his library; no doubt it was here that Davy found, in the last part of Beddoes' and Watt's *Considerations on the Medicinal Use and on the Production of Factitious Airs*, Latham Mitchill's remarkable paper which aimed to show that Priestley's dephlogisticated nitrous air was the principle of contagion.

It is obvious that the oft-repeated story which places Davy's first experiments with nitrous oxide as early as 1795, or even 1794, is fiction; for we have Davy's own words: "A short time after I began the study of chemistry, in March 1798, my attention was drawn to the dephlogisticated nitrous gas of Priestley, by Dr. Mitchill's Theory of Contagion."

Davy, intrigued by Mitchill's fantastic theory, submitted wounds made in the limbs of animals to the action of the impure nitrous oxide obtained by Priestley's method; he also hung portions of muscle fibre in the gas; there was no undue sepsis, no abnormal putrefaction in his specimens. Davies Giddy hastened to acquaint his friend Thomas Beddoes with the result of Davy's experiments.

At this time, Beddoes was preparing to proceed to the execution of a long-considered plan, the founding of a small hospital, having a limited span of life, to decide once and for all whether or no the gases held any place in the treatment of disease. Beddoes had need of a superintendent to take charge of his hospital and to assist in the laboratory; in the late spring or early summer of 1798, Davies Giddy suggested to him the name of Humphry Davy.

It is usually stated that Beddoes accompanied Professor Hailstone of Cambridge into Cornwall in the summer of 1798 to try and decide whether the formation of the Lizard rocks would throw any light upon the differences that existed between the Plutonian and Neptunist schools of geology, and that, while he was in Penzance, Beddoes met Davy and was so struck with him that he immediately offered him the post of superintendent of his institution. There is no truth in this story; the geological trip into Cornwall was made in 1791 while Beddoes was still Lecturer in Chemistry at Oxford, and it is sufficiently obvious from Davy's first letter to his mother from Bristol that he and Beddoes had never met until he took up his post as Beddoes' assistant.

In November 1798 Beddoes took a lease of two houses in the upper or north-west corner of Dowry Square; in the March of 1799 the laboratory was moved into the smaller of the two houses, and, on March 21, 1799, there appeared a notice in *The Bristol Gazette and Public Advertiser* that the Institution was ready to receive out-patients. These two houses still stand, forming Numbers Six and Seven Dowry Square in the Hotwells district of Bristol. They, as much as the Massachussetts General Hospital, should be the Mecca of every anæsthetist.

In that same month, March 1799, Davy prepared a large quantity of impure nitrous oxide obtained from the action of nitrous acid upon zinc, and purified it as best he could. On several occasions he inhaled this gas mixed with air; he found that the gas was irritant and apparently depressant, causing slowing of the pulse and a tendency to "fainting".

In the beginning of April, Beddoes drew Davy's attention to a paper written by the French chemist Berthollet. Berthollet enumerated various methods of preparing nitrous oxide, among them by means of heating nitrate of ammonia, essentially the same process that is used to-day. Davy did not, as is usually stated, invent this method, but he did improve it with the aid of James Watt. The apparatus that they devised for use at the Institution consisted of a glass retort, of approximately two or three quarts capacity, which led by means of a glass tube enclosed in tin plate to an air-holder, specially designed by Watt, the gas being received over water previously impregnated with nitrous oxide; all the joints were well "luted" to prevent ingress of air. The retort was heated by a "common air furnace" provided with dampers to regulate the heat and ensure that the temperature should not rise above 500° F. It is obvious from Davy's descriptions that the standard of purity of his gas was very variable; the figures that he gives tend to make the question obscure, but it would seem fair to suppose that his nitrous oxide varied from a low standard of 80% purity to a high standard of 95%, the only important impurities being varying proportions of nitrogen and oxygen.

In a letter of April 11 to *Nicholson's Journal* Davy writes: "In the Pneumatic Institution we have lately made some experiments on the nitrous phosoxyd (gaseous oxyd of azote), the principle of contagion of Mitchill. When it is mingled with 1/3 of phosoxygen (oxygen gas) animals live in it without suffering any injury. I have made two inspirations of it pure, without any disagreeable effects. I have breathed it mingled with an equal quantity of phosoxygen (oxygen gas) for some minutes; the effects produced by it were very peculiar . . ."

This letter would appear to refer to nitrous oxide manufactured by Priestley's method, for, on April 17, he again wrote to *Nicholson's Journal*:

"I have this day made a discovery, which, if you please, you may announce in your Physical Journal, namely, that the nitrous phosoxyd or gaseous oxyd of azote, is respirable when perfectly freed from nitric phosoxyd (nitrous gas). It appears to support life longer than common air, and produces effects which I have no time to detail at present. Dr. Mitchill's theory of contagion is of course completely overturned; the mistake of Priestley and the Dutch chemists, probably arose from their having never obtained it pure."

The curious nomenclature that Davy here uses is that which he suggests in his paper on light, which Beddoes, in the previous month, had published for him in the first and only volume of *West Country Contributions*. The theory was torn to pieces by the critics, and Davy was forced to withdraw; in after-years he stated that he would gladly resign all the credit that he had received for his later discoveries if only he could recall this ill-considered publication.

Armed with this new and improved method of manufacture, Davy embarked upon that long series of experiments, extending over a period of fifteen months, the results of which he published in July 1800 under the title *Researches Chemical and Philosophical Chiefly concerning Nitrous Oxide and its Respiration*. The manuscript of Davy's great work has disappeared, as have the major part of his rough notes but there remain two small note-books which contain a number of trial passages for his book, together with a mass of other matter, including some unpublished material on nitrous oxide.

Humphry Davy's book is divided into four Researches, the first two of which deal with chemistry, the second two with physiology. Taking the long view, that part of his work which deals with the chemistry of nitrous oxide is incomparably the more important, for it was this part of his work which directly influenced the course of events which led up to the introduction of anæsthesia; but the latter part of his book is by far the more interesting.

For the purposes of chemical analysis Davy obtained his nitrous oxide by the following method: "200 grains of compact nitrate of ammoniac were introduced into a glass retort, and decomposed slowly by the heat of a spirit lamp. The first portions of the gas that came over were rejected and the last received in jars containing mercury."

He sums up his findings as follows:

"Nitrous oxide is a gas unalterable in its constitution, at temperatures below ignition. It is composed of oxygene and nitrogene, existing *perhaps* in the most intimate union which those substances are capable of assuming. Its properties approach to those of acids. It is decomposable by the combustible bodies at very high temperatures, is soluble in double its volume of water, and in half its bulk of most of the inflammable fluids. It is combinable with the alkalies, and capable of forming with them peculiar salts. 100 grains of it are composed of about 63 nitrogene and 37 oxygene. 100 cubic inches of it weigh 50 grains, at 55° temperature and 30 atmospheric pressure."

Davy next embarked upon a long series of experiments designed to show the effect of the inspiration of nitrous oxide upon the blood and upon the products of respiration. It must here be said that the figures that he gives are to all intents and purposes useless, for he had accepted Lavoisier's figure of 27% as the oxygen content of air; nevertheless, he discovered many important facts in the course of these experiments.

He submitted cats and other animals to the action of pure nitrous oxide, and he found that they survived for about twice as long as when placed in hydrogen or water.

He also found that, although animals were very swiftly killed in pure nitrous oxide, they would live for a very considerable time in nitrous oxide mingled with oxygen, and that when the animal was taken out, apparently dead, it could be restored to life. In the course of these experiments, he gives us the first picture of nitrous oxide anæsthesia:

"Into a mixture of one oxygene, and three nitrous oxide, a small guinea-pig was introduced. He immediately began to struggle, and in two minutes reposed on his side, breathing very deeply. He made afterwards no violent muscular motion; but lived quietly for near fourteen minutes: at the end of which time, his legs were much convulsed. He was taken out and recovered."

From animals Davy turned to the human subject. He discovered that nitrous oxide was absorbed by the blood and he reckoned that two cubic inches of blood would absorb just over 0·2 of a cubic inch of the gas; when he submitted blood previously saturated with nitrous oxide to the action of oxygen, he found that the blood became oxygenated, even though it appeared that no nitrous oxide was lost from the blood; he had, in fact, discovered the basis of gas anæsthesia.

Next Davy himself breathed nitrous oxide, collected his exhalations and examined them; there was one great drawback to self-experimentation for the excitement stage of anæsthesia was quickly induced which did not favour accuracy of observation. He examined his "residual gas" in the following manner:

"After being transferred through mercury into a graduated cylinder, a small quantity of concentrated solution of caustic potash was introduced to it, and suffered to remain in contact with it for some hours; the diminution was then noted, and the quantity of gas absorbed by the potash judged to be carbonic acid. To the remainder twice its bulk of pure water was admitted. After agitation, and rest for four or five hours, the absorption by this was noted, and the gas absorbed considered as nitrous oxide. The residual unabsorbable gas was mingled over water with twice its bulk of nitrous gas; and by this means its composition, whether it consisted wholly of nitrogene, or of nitrogene mingled with small quantities of oxygene, ascertained."

Davy worked out the quantity of nitrous oxide absorbed in a given number of respirations, and the volume given off by the lungs. He found a discrepancy between the two figures which apparently led him to believe that some of the nitrous oxide was broken down in the blood stream to form nitrogen and oxygen, although in his rough note-book he has the note "it is absorbed by the blood and is not decomposed". It is very interesting that, at the end of *Researches* he says that nitrous oxide must be either "carried into new combinations, or given off by the capillary vessels through the skin"; a fact which does not seem to have been rediscovered until 1933.

Apart from nitrous oxide the chief interest of his investigation lies in the work that he did upon the respiration of atmospheric air; he held that air was decomposed in the blood stream, nitrogen being carried by the serum, and oxygen by the red corpuscles; the oxygen was combined with "charcoal" in the red corpuscles to form carbon dioxide, which, together with the nitrogen, was given off in the exhaled air. This part of Davy's theory has gone unnoticed; it marked a very real advance in the knowledge of respiration, particularly when we recall that Lavoisier's later work was at that time unknown in this country.

The last part of Davy's book, written in the form of a rough diary, covering the period March 1798–June 5, 1800, describes the sensations experienced by Davy and his friends when inhaling nitrous oxide. The gas started upon its chequered career in distinguished company, for the circle surrounding Beddoes and Davy was a brilliant one; the poets Southey, Coleridge and Wordsworth, James Watt the engineer, Tobin the playwright, the Wedgwoods, the Edgeworths, Joseph son of the great Priestley, all these inhaled nitrous oxide and, in the majority of cases, have left us, in their own words, a description of their experiences. It is difficult, from amongst this galaxy of talent, to choose a representative witness, for Davy's own classical description is perhaps too well known to bear repetition. Here is the record of one who can justly be called a master of words, a young doctor who came to work for a short time at the Institution, Peter Mark Roget of Roget's *Thesaurus*:

"The first effect was that of making me vertiginous, and producing a tingling sensation in my hands and feet: I seemed to lose the sense of my own weight, and I imagined I was sinking into the ground. I then felt a drowsiness gradually steal upon me, and a disinclination to motion; even the actions of inspiring and expiring were not performed without

effort; and it also required some attention of mind to keep my nostrils closed with my fingers. I was gradually roused from this torpor by a kind of delirium, which came on so rapidly that the air-bag dropt from my hands . . . and I suddenly lost sight of all the objects around me, they being apparently obscured by clouds, in which were many luminous points. I felt myself totally incapable of speaking, and for some time lost all consciousness of where I was, or who was near me. My whole frame felt as if violently agitated: I thought I panted violently: my heart seemed to palpitate, and every artery to throb with violence; I felt a singing in my ears; all the vital motions seemed to be irresistibly hurried on, as if their equilibrium had been destroyed, and everything was running headlong into confusion. My ideas succeeded one another with extreme rapidity, thoughts rushed like a torrent through my mind, as if their velocity had been suddenly accelerated by the bursting of a barrier which had before retained them in their natural and equable course. . . ."

The nitrous oxide was administered in small doses, generally about six quarts, and usually mixed with air; in the majority of cases the excitement stage of anæsthesia was the deepest level to be reached. Nevertheless, on occasion unconsciousness and, presumably, the stage of surgical anæsthesia was attained, in spite of the many assertions which have been made to the contrary. On only one occasion does Davy use the definite expression "consciousness was lost", but in many instances he speaks of "the pleasurable trance" or a "perfect trance" and it is obvious from the contexts in which these phrases occur that he was using another term to imply loss of consciousness. Robert Kinglake, physician to the Institution and author of a well-known book upon gout, gives a rather interesting description of his experience, which has some bearing upon this point, "its agency was exerted so strongly on the brain, as progressively to suspend the senses of seeing, hearing, feeling, and ultimately the power of volition itself".

From April until the end of July 1799, Davy inhaled nitrous oxide daily, frequently making several trials during the course of the same day. He found that surrounding circumstances had a marked effect upon his sensations: "I have often felt very great pleasure when breathing it alone, in darkness and silence, occupied only by ideal existence"; he gives the other side of the picture in words which should be written on the walls of every dental extraction room: "In two or three instances when I have breathed it amidst noise, the sense of hearing has been painfully affected by moderate intensity of sound."

This regular course of self-experiment had some injurious effect upon Davy's general health, although in the privacy of his note-book he states that his illness was not due to the gas, but to "certain moral causes". Some of the general symptoms that he describes in *Researches* are "increased sensibility of touch: my fingers were pained by anything rough, and the tooth-edge produced from slighter causes than usual. I was certainly more irritable and felt more acutely from trifling circumstances." This passage is of historical interest, for it was later to be used by Charles Jackson, the Boston chemist who claimed to have discovered the anæsthetic action of ether, as a proof that nitrous oxide had no anæsthetic action.

Another result of too frequent inhalation was that Davy became a nitrous oxide addict: "I ought to have observed that a desire to breathe the gas is always awakened in me by the sight of a person breathing, or even by that of an air-bag or an air-holder." It would appear that he easily broke himself of his habit, for there is no evidence that he inhaled nitrous oxide after he went to London.

From the beginning of August 1799 onwards, Davy inhaled nitrous oxide only for pleasure and for the purpose of special experiments. He had come to the conclusion that the effect was stimulating, but he was by no means certain that nitrous oxide was exactly similar in its effects to the ordinary stimulants. On December 23, 1799, he decided to perform an experiment, the purpose of which was to try and find out whether or no the inhalation of nitrous oxide would increase the debility produced by over-stimulation with a known agent. For this purpose he drank wine to the point of intoxication; the first effect was very like "the first stage of nitrous oxide excitement" but within an hour he became insensible. He was awakened by headache and nausea, which persisted even after the contents of the stomach had been ejected. While in this condition, he breathed nitrous oxide for a minute and a half but, as he experienced no sensations, he thought that it must have been very impure. Then he breathed oxygen, which had no effect at the time, but he thought afterwards that he was a little better.

As he still suffered from very severe debility and headache, he examined some nitrous oxide that had been freshly prepared and, finding it to be very pure, he breathed it; he was unconscious of headache after the third inspiration, "the usual pleasurable thrilling was produced, voluntary power was destroyed, and vivid ideas rapidly passed through my mind". Some nausea and headache returned after the effect of the nitrous oxide had passed off, but the degree of depression was not increased. Therefore the debility resulting from intoxication was not increased by the action of nitrous oxide.

The account of this experiment occupies some few pages of *Researches;* his immediate note, written down in his rough book, reads simply: "On December 23rd I breathed after a terrible drunken fit a large quantity of gas 2 bags & two bags of oxygen it made me sick."

On December 26 he embarked on a still more strenuous experiment, no less than to submit himself to "the most extensive action of nitrous oxide compatible with life" for the purpose of deciding whether the prolonged action of nitrous oxide would produce effects similar to those experienced after prolonged stimulation with alcohol.

For this purpose he enclosed himself in an airtight box into which nitrous oxide was introduced in quantities of twenty quarts at a time. He remained in the box for an hour and a quarter, at the end of which time he experienced "a great disposition to laugh, luminous points seemed frequently to pass before my eyes, my hearing was certainly more acute and I felt a pleasant lightness and power of exertion in my muscles. In a short time the symptoms became stationary, breathing was rather oppressed, and on account of the great desire of action, rest was painful".

He then came out of his box and immediately breathed twenty quarts of pure nitrous oxide out of a bag. His sensations, as recorded in *Researches*, have been described on many occasions; in his note-book he gives a rather different account: " . . . I seemed to be a sublime being, newly created & superior to other mortals. I was indignant of what they said of me and stalked majestically out of the laboratory to inform Dr. Kinglake privately *that nothing existed but thought*. I was they said near three minutes at this. I then went upstairs and breathed the remainder for a similar time—the sensations were the same, a new tribe of perceptions, which I am conscious existed from their connection with words became connected with my visible and tangible impressions, new organs were apparently created, there was an exquisite pleasurable thrilling in the extremities. I continued in a state resembling slight intoxication for an hour or two afterwards. Had less disposition to action and thinking than usual—but no languor or depression followed—I eat my dinner heartily and felt no inclination to sleep which I generally do. I found [myself] disposed to experiment immediately after dinner. I have been in good spirits all the evening, I have eat a good supper and have rather more industry than usual as I have [written] almost the whole of this since eight oclock—it is now I believe much after midnight & I feel no disposition to sleep."

After a good night's rest he awoke in a happy frame of mind. There was, therefore, no resemblance between the effects of prolonged indulgence in alcohol and prolonged stimulation with nitrous oxide. From now on, Davy and Beddoes differed in their views of the nature of nitrous oxide; Beddoes, obsessed as he was by the brunonian theory of medicine, regarded nitrous oxide as a stimulant pure and simple, "oxygen in a more perfect form", a more perfect principle of irritability. But his researches into the nature of nitrous oxide had led Davy to believe that the brunonian theory was fallacious, "the common theory of excitability is most probably founded on a false generalisation". Partly because of this and partly because Davy was annoyed that Beddoes' indiscriminate enthusiasm had flattered him into the premature publication of his discredited theory of light, a rift developed between the two; for this reason Davy never published the very gracious dedication of his work to Thomas Beddoes, which may be found in his note-book, contenting himself with a dry acknowledgment of his obligations. The rift was not a deep one, for it was to Davy that Beddoes wrote those well-known words in which he expressed his last heart-broken confession of failure.

Nevertheless, although he recognized that there was some difference, Davy regarded nitrous oxide as "analogous" to the ordinary stimulants; "both increase the force of circulation, produce pleasurable feeling, alter the condition of the organs of sensation, and in their most extensive action destroy life". He considered that depression did not follow stimulation with nitrous oxide because "a smaller quantity of nutritive matter may be required than in ordinary stimulation, and exhaustion from deficiency may not result".

To us, the supreme interest in Davy's work lies in his finding that nitrous oxide alters "the condition of the organs of sensation". Quite early on in his investigation he had noticed this fact; when a patient, suffering from a painful rheumatic affection, was made to inhale nitrous oxide, a pleasurable feeling was induced and the pain disappeared; nor did it recur until some few minutes after the inhalation had been discontinued. Beddoes chose to disregard this property of the gas; to his mind, "hydrocarbonate" and carbon dioxide were the sedatives; oxygen and nitrous oxide their antitheses. But Davy, by self-experiment, was led to the truth; during his course of regular inhalation he found that on two occasions headache was removed by the gas, and then, while he was only inhaling nitrous oxide on special occasions, there occurred that magnificent opportunity to make trial of the pain-allaying effect of the gas which provides one of the few well-known passages in Davy's sadly neglected book.

"The power of the immediate operation of the gas in removing intense physical pain, I had a very good opportunity of ascertaining.

"In cutting one of the unlucky teeth called *dentes sapientiæ*, I experienced an extensive inflammation of the gum, accompanied with great pain, which equally destroyed the power of repose and of consistent action.

"On the day when the inflammation was most troublesome, I breathed three large doses of nitrous oxide. The pain always diminished after the first four or five inspirations; the thrilling came on as usual, and uneasiness was for a few minutes, swallowed up in pleasure. As the former state of mind however returned, the state of organ returned with it, and I once imagined that the pain was more severe after the experiment than before."

There can be no doubt that, when Davy became convinced that the action of nitrous oxide was capable of turning acute physical pain into mental pleasure, he considered that, if only he could reason the matter out, he had found the answer to the eternal problem of pleasure and pain. We catch a glimpse of this belief in *Researches* but we gain a far better view of his absorption with this problem in his rough note-book wherein he devotes a large amount of space to its consideration.

One day in the spring of 1800 (it has proved impracticable to fix the exact date) Davy was writing an essay upon the pleasures and pains of sense; quite suddenly, a practical application of his discovery occurred to him; he broke off his argument and wrote across the page:

"removing physical pain of operations."

boxing the words in between two lines as though he regarded them as of importance.

At the end of *Researches* Davy wrote notes of a few suggested uses to which nitrous oxide might be put; unstressed amongst these suggestions occur the historic words:

"As nitrous oxide in its extensive operation appears capable of destroying physical pain, it may probably be used with advantage during surgical operations in which no great effusion of blood takes place."

It is sometimes stated that Davy made only a casual observation of the fact that nitrous oxide appeared to destroy pain and that he attached no importance to his finding; in fact he devoted a very considerable amount of thought to the problem of why nitrous oxide, which appeared to have so stimulating an action, should allay pain to a degree never reached by the recognized sedative gases, carbon dioxide and "hydrocarbonate". Finally he solved his problem, although he never published his solution. The theory which he propounded may perhaps be regarded as the first theory to account for the phenomenon of anæsthesia: "Sensible pain is not perceived after the powerful action of nitrous oxide because it produces for the time a momentary condition of other parts of the nerve connected with pleasure."

Davy's book was well received; it was reviewed favourably and at length in the medical and scientific press; indeed, his work on nitrous oxide was regarded as of sufficient importance to warrant his appointment by the Managers of the Royal Institution to the post of Assistant Lecturer in Chemistry with the promise of future advancement to a Professorship. Nor, with all due respect to the *Dictionary of National Biography* and other weighty authorities, did Davy ever regard his researches into nitrous oxide as "the dreams of misemployed genius"; the context in which these oft-quoted words occur makes it obvious that he was referring to his discredited theory of light. But, with the publication of his book, Davy looked upon his work on nitrous oxide as ended; after he went to the Royal Institution he gave one short course of lectures on Respiration, in the course of which he demonstrated the effects of nitrous oxide, but he performed no further researches on the gas after he left Bristol for London in March 1801, exactly two years after the Pneumatic Institution had first opened its doors, exactly at the end of the term which Beddoes had set for its useful existence.

Nevertheless, it is possible that Davy once again crosses the pages of the history of anæsthesia. In the year 1818, in the *Journal of Science and the Arts*, the official organ of the Royal Institution, there appeared an unsigned annotation drawing attention to the similarity between the action of nitrous oxide and of ether when inhaled. This note has always been ascribed to Michael Faraday; although no evidence has ever been adduced in support.

If the note is examined, it appears most unlikely that Faraday wrote it; the subject matter does not suggest Faraday; Faraday was a careful writer and always signed his articles; this note is carelessly written and is unsigned. Both the subject and the diction are reminiscent of Davy; recently no less an authority than Dr. Charles Singer has informed me that he believes Davy to be the author.

So much for Davy's work: how far did this work influence the introduction of anæsthesia? At the time when his book was published, only one man that we know of paid any attention to his remarks on pain; that man was Davy's close friend, Samuel Taylor Coleridge, the poet. In this sense, Davy's discovery of anæsthesia was abortive, a fact which may seem

strange to us with our twentieth-century outlook on suffering, but which is not so strange when we consider the mentality of the eighteenth-century Englishman. Behind that elegant eighteenth-century façade there dwelt a callousness, a brutality almost unprecedented in history; such advance toward a broader humanitarianism as had been made in the 1770s and 1780s had been largely counteracted by the inevitable reaction induced by the war with revolutionary France. Nor did the name of Pneumatic Medicine inspire belief; interesting although Davy's findings were to chemists and scientists, the average physician would have looked upon his theories as the scatter-brained enthusiasm of one who still believed in the dead hopes of Beddoes and his school of pneumatic physicians. Thus we cannot blame Davy for the fact that he did not introduce anæsthesia, any more than we can blame his contemporaries because they did not accept the definite proposal that he threw out to them.

If we turn the pages of history forward for nearly fifty years we see a very different picture. Man had achieved a new attitude towards suffering; the pain of surgery had become an anachronism in a world bred in the humane tradition of such men as Wilberforce and Thomas Arnold. Hickman, Collyer, Elliotson, Esdaile among others had embarked upon that desperate though unavailing search for a means of allaying the pain of surgery; the world was awaiting and eager to accept the great gift of ether from Thomas Morton.

But it was no divine revelation which suggested anæsthesia by means of ether to Morton. Morton, a comparatively uneducated man, learned of ether from Charles Jackson, learned of the fact of anæsthesia from his one-time partner Horace Wells. Wells, in turn, learned of nitrous oxide from the itinerant lecturer Gardner Quincy Colton and Colton, in his turn, gained his knowledge of nitrous oxide from Humphry Davy; for the whole knowledge and teaching of nitrous oxide depended upon Davy's work. We find that, at the University of Edinburgh, the chemistry lectures of Dr. Hope contain references to Davy's researches on nitrous oxide; far away in Pennsylvania, a student uses the phrases "What concatination of ideas", "Nothing exists but thought", to illustrate the extraordinary effect of nitrous oxide; both these phrases occur in Davy's *Researches*.

Undoubtedly it is upon this point that the importance of Davy in the history of anæsthesia rests, nevertheless there are one or two less important, but perhaps more dramatic, points which suggest that his influence was more direct than is generally allowed.

Colton published advertisements for his lecture in Hartford, Connecticut, that lecture which induced Horace Wells to experiment with nitrous oxide in dentistry. In the course of this advertisement, Colton uses the words: "Robert Southey (poet) once said that 'the atmosphere of the highest of all possible heavens must be composed of this gas'." These words are part of a private letter from Southey to Davy, which was first published in the year 1858, fourteen years after Colton quoted them. It would take too long to describe the search that has been made in an endeavour to discover from what source Colton derived this information. My conclusion is that he could only have obtained it from Thomas Beddoes' forty-five page pamphlet *Notice of some Observations made at the Medical Pneumatic Institution* or from the review of that pamphlet which appeared in *Nicholson's Journal*, both of which contain these words and both of which were published in the autumn of 1799. Not only does this give a direct link between Colton and the work done at the Institution, but it also proves beyond doubt that Colton had made a very extensive study of the literature on nitrous oxide.

Then, too, we can obtain some suggestive information from the evidence of both Morton and Jackson. Edward Warren, Morton's agent, recognized in Davy the man who first discovered the anæsthetic power of nitrous oxide, though he did so, not to glorify Davy, but to dispose of the claim of their chief rival, Horace Wells.

Jackson went further. He claimed that in 1838 he had made trial of nitrous oxide and had found it ineffectual; he even went so far as to misquote Davy's words in an attempt to show that he was mistaken in believing that nitrous oxide would allay pain. Yet, charlatan as he was, unreliable witness as he has shown himself, Charles Jackson, alone among the later pioneers of anæsthesia, has acknowledged his indebtedness to Davy; for, on the subject of anæsthesia, he writes:

"I have in former publications stated, as I do now, that my attention was first awakened to this subject while a student of medicine, by reading Davy's researches . . ."

Thus from Morton through Wells and Colton, and through Jackson, through the nitrous oxide demonstrations, and perhaps through the ether frolics as well, the chain leads back to Humphry Davy; Davy, who, by his great work on nitrous oxide, fired a train of events which was destined to culminate in the introduction of anæsthesia; without his work, those events must have taken a different course; in this sense his influence in the story of anæsthesia is overwhelming.

Not only this. Humphry Davy, first of all men, discovered the anæsthetic action of nitrous oxide, Humphry Davy, first of all men, suggested a practicable means of allaying the agony of surgery. Humphry Davy discovered anæsthesia.

Section of Neurology

President—JULIAN TAYLOR, C.B.E., M.S., F.R.C.S., F.R.A.C.S.

[*March* 2, 1950]

DISCUSSION ON SPEECH DEFECTS IN CHILDREN

Dr. Henry Miller[1].—During the course of the past two years Miss Muriel Morley, Dr. Donald Court (University Reader in Pædiatrics) and I have held a weekly clinic at which we have reviewed examples of all the disorders of which I shall speak. Our aim was threefold. We hoped first to do something to define the commoner patterns of speech disorders in an endeavour to improve the accuracy of prognosis in the individual child; secondly to clarify our concepts for purposes of undergraduate teaching; and thirdly to formulate some of the ætiological problems involved. Our contribution consists in the posing rather than the answering of some questions in this connexion.

The problem is not merely academic, though the precise extent of speech disorders amongst school children in Great Britain is unknown. In 1945 Miss Morley made a survey of 12,000 Gateshead school children between the ages of 5 and 14 years, and found that in that year 3·3% of these children were suffering from substantial speech defects. During the past ten years 1,500 cases have been seen at the Children's Speech Clinic in Newcastle and Table I shows the broad descriptive categories which Miss Morley was using during this period:

TABLE I.—% DISTRIBUTION OF 1,500 CASES REFERRED TO A CHILDREN'S SPEECH CLINIC

Stammering	40
Defective articulation with no evident physical lesion	31
Cleft palate	16
Deafness	7
Mental deficiency	4
Cerebral palsy	2

This analysis is based on selected material referred for specific attention to a speech defect. It certainly underestimates the role played by mental deficiency in relation to the speech defects met with in general medical practice, because recognizable cases of mental backwardness are not usually referred to a speech clinic. For somewhat similar reasons it underestimates also the role of cerebral palsy; while, because of a special interest in the department, the proportion of cases of cleft palate is unusually high. Nevertheless, the figures are of interest and one point of practical importance is that they show the high proportion of defects which are potentially curable, and the relatively smaller size of the group in which an organic lesion can be clearly identified.

It soon became apparent that this simple classification was inadequate. The group labelled "defective articulation without physical lesions" was found to contain at least two conditions of widely differing prognosis. Further, a number of children with receding and unobtrusive but unmistakable spastic diplegia came to light; while the fourth group of cases in which a speech defect was associated with deafness was subdivided with greater precision.

The number of classifications available in the literature of the subject is enormous. Many of them are the work of observers who, for professional reasons, tend to regard speech as

[1]With gramophone illustrations and case histories by Miss Muriel Morley.

an infinitely subdivisible entity. Some of these are highly complex and over-mechanistic, employing neologistic terminology and having no rational basis in physiology.

The tentative working classification which we have employed is shown in Table II:

TABLE II.—WORKING CLASSIFICATION OF SPEECH DISORDERS IN CHILDREN

A.	*Deafness* ..	(1) Congenital nerve deafness: (*a*) Severe for all frequencies (*b*) Partial or high-frequency deafness (2) Acquired nerve deafness (3) Middle-ear deafness
B.	*Dysarthria* ..	(1) Due to local anatomical lesions (2) With neurological signs of cerebral disease or mal-development (3) Unassociated with abnormal neurological signs elsewhere
C.	*Developmental Aphasia*	(1) Predominantly expressive aphasia (2) Predominantly receptive aphasia: (*a*) Dyslexia (*b*) ? Congenital auditory imperception (3) Delayed development of speech
D.	"*Dyslalia*" ..	Defects of consonant substitution and omission
E.	*Stammering*	

This attempt at classification has grown out of our day-to-day experience and is, as far as possible, conceived within the framework of accepted neurological terminology. Attempts to break down a complex and closely integrated function such as speech cannot be pressed too far, and many cases show mixed features. The diplegic child for example frequently appears to show not only the familiar spastic dysarthria but also a developmental aphasia. Similarly in some mentally backward children delay in the development of speech is accompanied by the substitution defects to which we have limited the term" dyslalia".

It is unusual for loss of hearing in cases of *severe congenital nerve deafness* to be complete, but in marked cases there is rarely any development of speech. The deafness is usually obvious, and these children should be recognized early and arrangements made for their training in lip-reading by the mother from the age of 3, and for their special education from the age of 5.

Cases of *high-frequency deafness* present real difficulty. They are often missed. Above all it is necessary to be sceptical of the mother's statement that the child is not deaf. This is a natural error on her part because the child is often alert and intelligent and can hear the closing door or the passing car. He may even listen with appreciation to music on the radio, but he shows little interest in stories or conversation. Repeated audiometric tests reveal a partial deafness to account for the retarded development of speech, which is characterized in particular by defective sibilants.

These children are in grave danger of being classed as intellectually subnormal.

Acquired nerve deafness may be partial or complete and usually results from the inflammatory damage of meningitis, measles or some similar infection. When this occurs during the first five years of life, it causes faulty development or deterioration of speech. The result depends both on the age of occurrence of the deafness and on its severity, but in severe cases the problem is the same as in congenital deafness.

Bilateral persistent middle-ear deafness severe enough to hamper the development of speech is less common before the age when speech is developed than in later years. The deafness usually tends to be less constant, and unless it is very severe it is a relatively rare cause of speech defect.

Cleft palate is the only important local anatomical cause of dysarthria, and apart from stressing the necessity of obtaining an effective closure of the nasopharynx this group need not detain us.

Amongst cases of dysarthria due to generalized neurological disorders we include children with *spastic diplegia* and allied defects such as athetosis, and those case of developmental apraxia of which we have read but which we have not met personally. The usual finding is, of course, a spastic dysarthria. Again speech is slow to develop, and stiffness and clumsiness of the muscles of tongue and lips render articulation slurred, indistinct, and often explosive.

Again there is a tendency in severe cases to attribute the lack of speech, the often rather vacant expression, and the emotional lability, to mental defect. One of our most dramatic cases illustrates this well:

This was an only child aged 16, whose mother died when he was 7. At this time he could neither talk nor walk and was regarded as mentally defective and sent to a special institution. One of the nurses was interested in the boy and doubted the diagnosis of mental defect. By a remarkable coincidence she left the hospital and later married the boy's father. They decided to bring him home.

He was then 14 years old and still unable to walk and talk. When first seen by us eighteen months later he could, through the efforts of his stepmother, walk, dress himself, talk and read, and had secured a job delivering newspapers.

The condition was one of severe spastic diplegia with educational backwardness. Speech was clumsy but intelligible. When seen again three years later he was still delivering papers, attending evening classes, and making good progress in writing and composition. Speech and walking had continued to improve.

This also shows that even in speech defects with a clear basis in disordered physiology and defective anatomy the influence of environmental factors is very great.

There is, however, a group of cases of *dysarthria without abnormal neurological findings outside the speech mechanism*, usually less severe than those above, but in other ways apparently identical, and similarly slow to respond to treatment. In this group neither history nor examination reveals evidence of any more widespread neurological disorders. I will return to them later.

Cases of *developmental expressive or motor aphasia* occasionally occur in association with cerebral agenesis but the condition may be found as an isolated defect in a child with good hearing and understanding for speech. Some of these children are mentally backward, but in others the defect of motor speech seems out of proportion to the degree of intellectual retardation, and in a few the defect is even more specific, and the intellectual level apparently normal.

We have seen one case of *dyslexia* as an isolated defect and several others in which it was apparently out of proportion to a co-existing degree of mental backwardness. We have not seen any cases of pure *congenital auditory imperception* (*see below*).

We were doubtful about the validity of *delayed development of speech* as a special category. We have used it to describe a total failure of speech development—a severe failure of maturation of speech function on both the receptive and expressive sides, without deafness, but often with some associated articulatory defect. This is the type of speech defect most often encountered in frank mental defectives.

Dyslalia we have removed from the original category of defective articulation without evident organic lesions, and we use the term in a more specific sense than most observers—for a common, essentially circumscribed, reversible, and rapidly remediable defect of consonant substitution or omission.

Of stammering, certainly the commonest and most important speech defect, we have made no detailed study.

Three problems have particularly excited our interest:

The first concerns those cases which show a *dysarthric defect in the absence of any detectable neurological lesion elsewhere*. Amongst cases initially grouped under this heading we discovered a small number in which history and examination revealed clear evidence of minimal diplegia. In some such cases retrospective enquiry revealed that the child suckled poorly, or walked late or unsteadily, or showed early clumsiness with the hands, while on physical examination there was some degree of spasticity. In a number of patients, however, a very similar dysarthria was found with no other evidence whatever of cerebral disease or maldevelopment.

The precise cause of the defect in this group of cases is not clear but it seems to us likely to have some structural basis. The defect is constant in type in each case, and appears to be due to physical clumsiness in the peripheral mechanisms of speech. The number of children we have seen with defects of this type is not great enough for us to be positive but it is our impression that these children develop speech late, and certainly response to treatment is always very slow. In different cases the faulty movements may affect mainly lips, tongue, soft palate, pharynx, or larynx, inco-ordination of which may be evident on examination but shows itself only when the muscles are used for the rapid and complex co-ordinated movements of speech. For other purposes muscular co-ordination seems adequate. The difficulty may be most noticeable in joining a consonant to a vowel or in the co-ordination of phonation and articulation. Speech may be fairly normal when it is slow and deliberate, but neuromuscular control seems to be inadequate for the rapid movements of normal speech. The defect may be mild or severe. It shows little spontaneous improvement, and even with treatment may persist into adult life. Sometimes it is familial.

The lesion in these cases may be some form of local cerebral agenesis analogous to, but more limited in extent than, that found in cerebral diplegia.

The second condition which interested us was *congenital auditory imperception*. We began this review with an open mind, and indeed at first we thought we had some examples of this defect in our series. Repeated audiometric tests have whittled them away to nothing, for every example has proved to have a considerable degree of partial deafness. It is true that in some of them the failure of understanding of speech seems disproportionate to a degree of hearing deficit which in other subjects is not accompanied by such a pronounced

failure of understanding, but this is a far cry from attributing the defect wholly to a specific agnosia of central origin.

We would be interested to hear how far this is a general experience, and whether the existence of congenital auditory imperception is authenticated.

The third and last problem concerns the defect to which we have deliberately limited our use of the term *dyslalia*, a term often used more vaguely. By it we refer to a fairly clear-cut group of children with normal hearing, early development of language, without clumsiness of lips or tongue, but with varying degrees of consonant substitution or omission, which may be so severe as to render speech completely unintelligible. This defect occurs at all intellectual levels but many of these children are of high intelligence.

These cases tend to spontaneous recovery, which can certainly be accelerated by treatment. Most of them can be cured in from six to twelve months, and should obviously receive treatment before the time comes for them to go to school.

We do not know the nature of this defect, which can be so severe and yet is so easily remediable. What seems clear is that these children have normal hearing and understanding for speech. They speak easily, and have an excellent flow of language. The condition occurs during the early and rapid period of language development. These children think they are talking normally, and are bewildered that they are not understood, so much so that in desperation they may stop talking altogether. It is our impression that they do not understand their own speech when it is played back to them, but it is difficult to be absolutely sure of this because they are quite unduly upset by the experience.

In some ways the condition seems comparable with that often seen at a certain stage in the learning of foreign language, when vocabulary outstrips accuracy in pronunciation, and when faulty habits of speech are acquired unconsciously and with such ease, often to prove obstinate in the absence of careful re-training. Is this condition in the child associated with defective imitation of sounds inaccurately perceived, and reinforced by repetition and habit? Or must it be interpreted psychodynamically as yet another infantile fixation?

Miss Muriel Morley: [Records were played to illustrate the types of speech defect described.]

(1) The speech of a child, 8 years of age, with defective hearing for the higher frequencies of sound. Speech was late in developing and at 7 years was not intelligible. She used gesture and understood speech only when she could see the speaker's face.

(2) The speech of a girl, aged 6 years, with spastic diplegia. She began to speak at 2½ years and has good language development. Consonants in isolation are normal, but speech is dysarthric, and at times explosive.

(3) A girl, aged 4 years, has several consonant substitutions and explosive dysarthric speech. Movements of the upper lip, tongue and soft palate are poor. There is no demonstrable neurological lesion otherwise.

(4) Dysarthric speech in a family of 4 brothers and 4 sisters. The ages now range from 60 to 72 years. There is no known familial history of speech defect, hearing or mental defect. Three have normal speech, one has defective speech, and four still have unintelligible speech.

(5) A boy, 6 years, has an I.Q. of 117. Understanding for speech is normal, but speech was unintelligible as he omitted most consonants. Speech was again recorded after 10 weekly clinical attendances, showing the marked improvement in a short time which is common in this type of case (Dyslalia).

Dr. Macdonald Critchley: Dr. Miller's classification of speech disorders in childhood is very welcome, because the literature upon the subject is particularly muddled. Manifestations of specific speech retardation, of defective articulation, stammering, dyslalia, the imperfect speech of the deaf or partially deaf, the halting speech performance of the mentally backward, and the loss of speech due to acquired brain disease are apt to be hopelessly confused. Even the nomenclature is unsatisfactory, for "aphasia" when used in pædiatrics seems to mean something quite different to the speech therapist than to the neurologist.

I propose to deal solely with *aphasia* in the proper sense of the word, that is to say, with a deterioration in language performance as the result of cerebral affections. Here the literature is meagre in the extreme, and far from adequate, being descriptive rather than judicial. There is a need for a thoughtful, reasoned, and authoritative study of this interesting though difficult problem. In order not to muddy the waters still more, it would be best to omit altogether those problematical cases labelled "congenital aphasia", which have been assumed to represent an inborn defect of comprehension or execution—congenital word-blindness, congenital auditory imperception, congenital dyscalculia, and the like. We are still so uncertain as to their proper niche in neurology that for the time being at any rate they might well be set aside.

There are a number of reasons why aphasia, in the strict sense, should be different in the child from that in the adult, not only as to its characters but more particularly as regards its essential nature. Guttmann's paper (1942) served rather to stress the points of similarity.

Every aphasia is an affection of the faculty of language, and, therefore, a disorder of thought. The problem of childhood aphasia must therefore entail a discussion of language in the child, and hence, of a child's processes of thinking. The very term "aphasia in the *child*" is virtually meaningless, for thought and language are vastly different in the second semester than in the first; in the second year of life than in infancy. Indeed during the whole pre-puberty period, thought and language are faculties which are undergoing rapid change and development. If these ever-expanding activities are ablated or disturbed, the resulting manifestation will vary according to the age at which the lesion appears. Aphasia in the school child, in the youngster, in the toddler, and in the infant are problems of quite different nature.

In a child, speech is a new acquisition, and like most recently evolved faculties, it is vulnerable. Like an orchard blighted by a late frost, we find that a child loses its speech pretty easily, and he may show a taciturnity or even a mutism for a variety of reasons. In such cases there may be no focal disease of the brain but only a presumed thinly spread minor cerebral affection. I have in mind the poverty of speech in chorea. Speech may be lost even in disorders which do not directly involve the nervous system, e.g. in some febrile and toxi-infective states. But these affections of speech are not to be included among the true aphasias. Though in some ways vulnerable, speech in the child is also a highly resilient faculty. Hence a considerable restitution of function is always possible and speech may return to normal with little delay. Even in the aphasias due to focal brain lesions, a permanent speech defect is rare.

In the adult, language bears a relationship to thought which is quite unlike that occurring in early life. That is to say, the "uses" or "functions" of speech are quite different in the child from what they are in the adult. In the grown-up, speech is largely (though not entirely) a means of conveying ideas and feelings to others. This is not so in the child. The transitive functions, requiring the presence of an interlocutor, are less obvious, and a child may talk aloud as a means of self-expression and as a form of play. To the young child speech is a newly acquired toy rather than a familiar instrument over which he has attained mastery. As Fowler Brooks (1939) put it, "children do not use language chiefly to communicate, or to attain social ends, but to express personal power, to call attention to self-display, to command, request, and contradict".

More precisely we may recognize various stages in the development of speech in the infant and young child. A preliminary period of screaming (indicative of discomfort) leads on to a stage where both discomfort and comfort sounds are emitted. Then comes about a protracted phase of babbling in which the child makes sounds as a form of play. Thus he gains some degree of mastery over his phonetic utterance, and noises begin slowly to attain symbolic value. This is the beginning of baby-talk with its reduplications, its imperfect articulations, its primitive but developing syntax, its tussle with the difficult concept of shift-words, pronouns and generic terms. Gradually as the first two years slip by, the stage of "little speech" is attained which is retained but in steadily evolving nature until around puberty. The "gradualness" of the evolution is imperfect, for as a child grows, his range of vocabulary from time to time seems to undergo temporary set-backs. Even at this comparatively late stage, "much of his conversation may still be self-assertive. He ask questions, answers questions, argues, objects to suggestions, agrees to do things, and tells other children what to do or what not to do" (Fowler Brooks).

It must not be thought that these various stages—screaming, babbling, baby-talk, &c.—are clear-cut, well-defined phases like the stratifications of a Neapolitan ice. Indeed we know so little about the manifestations as well as the nature of childhood speech, that any dogmatic discussion of speech pathology is vain.

To probe deeper into the growth of speech in the child demands an enquiry into his thinking processes. The beginnings of awareness usher in a sort of autistic regime, which only very slowly, by a process of gradual socialization, leads to a mature type of "thinking in words". There is a lengthy intermediate period in which egocentric thought obtains, with a marked predominance of concrete over abstract ideas. Hence we find the vocal expression of these stages of thought in interjectional cries, in egocentric speech and finally in the newly attained adolescent speech, now grammatically and phonetically acceptable. As Vigotsky (1939) has said, there is an interesting paradox in the child between the growth of speech and the growth of ideas. With regard to the former there is a progressive expansion in vocabulary; while on the semantic side the child starts from the whole, from a meaningful complex, and only later beginning to master the separate semantic units and the meaning of separate words. "The semantic aspect develops from the whole to the particular, from

sentence to word; the external aspect however, from the particular to the whole, from word to sentence."

If then the semantic background of a childhood aphasia is difficult, fluid and intangible, we must also admit that the same is true for the provocative lesion. Aphasia may arise in the child from a focal lesion of the brain or from one which is diffuse. The lesion may be static (e.g. embolism), regressive (e.g. trauma), or progressive (e.g. tumour). These are factors which must be considered when the resulting aphasia is studied. Focal, non-progressive lesions of the brain are rarely followed by a permanent speech-defect. How often do we see a patient with a congenital or infantile hemiplegia who is also aphasic? The severest and most intractable cases of childhood aphasia are encountered in diseases where the lesion is diffuse rather than focal, progressive rather than stationary. I refer to such conditions as Schilder's encephalitis, the cerebral lipoidoses, the dementia præcocissima of Sancte de Sanctis, and the juvenile dementia of Weygandt and Heller.

What of the clinical pattern of aphasia in the child? We have but little information. My impression is that aside from the basic similarities, there are some points of contrast with the adult varieties. I would like to suggest the following clinical features as distinguishing the aphasias in early life:

Logorrhœa, or an uninhibited torrent of speech, is *rare*.

Jargon-aphasia is *uncommon*.

Simple *naming-defects*, as in amnesic aphasia, are *not usual*.

Dysarthria is common, but differs from that which accompanies aphasia in the adult, by reason of a *dyslalia* (amounting even to an idioglossia) representing an avoidance of difficult sounds and the substitution of easy ones.

Reduplications of simple sounds are *common*, as are speech-iterations. These latter may take the form of a word, a phrase, or neologism.

Syntactical defects are common, leading to a telegrammatic economy of speech—the "*para-grammar*" of Fröschels.

Lastly I would submit quite tentatively that in children with aphasia we see something which approximates to Jackson's dissolution of a cerebral function, in a way which is less demonstrable in the adult. A recent faculty—still at a relatively simple stage—is disintegrating, and in so doing tends to slip down some of the steps which it has but lately ascended. This cannot be said of the adult with aphasia. But in a child we find a reversion to the syllabic reduplications of an earlier age, an off-loading of the more difficult and recent phonetic accomplishments, and an upset in grammar with a return to the almost exclusive use of nouns.

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Dr. E. M. Creak: In this contribution I have deliberately limited myself to one or two observations concerning the emotional problems associated with children's speech, and will consider disorders affecting speech rather than defective speech as such.

Apart from recently acquired stammering in war neuroses, most stammerers are seen after the habit has become well established, and sometimes after many other treatments have failed.

Far too often an attempt is made to treat the stammer, and not the stammerer. Nevertheless, in dealing with the anxiety neurotic, or hysteric who stammers, it is equally possible to lose sight, or indeed never get around to seeing, why he stammers instead of being enuretic or having asthma, or failing in school. If he reaches us as an adult, with many years of habituated stammering behind him, well overlaid with compensatory mechanisms, it is impossible to rediscover in any vivid way, without deep analysis (and not always then), the roots of his choice of speech as the peg on which to hang his neurosis.

My purpose therefore is to direct attention to certain behaviour abnormalities in relation to speech, and to indicate some ways in which disordered speech is utilized as an expression of maladaptation in children.

Before going on to consider the importance of speech to the young child, I would like to refer briefly to the oral activities which precede it. It is hardly accurate to regard the mouth as the organ of speech any more than the tongue, lips or larynx, but there can be no doubt that children think of speech as coming from the mouth and they indicate this very clearly in their drawings. My impression is that in their body fantasy, they primarily think of speaking with their mouths.

Long before this happens, however, the mouth has been a highly active and highly

sensitive part of the body concerned primarily with the intake of nourishment, secondarily as a highly sensitive region for feeling things, probably by tactile sensation rather than by taste. Since this method of apprehending things is so soon superseded by a higher development of tactile sensibility in the finger-tips, the feelings connected with it rarely seem to reach the same intensity as those relating to the process of feeding.

Perhaps the most important thing to note in connexion with the primary mouth activity is that the satisfaction of an instinctive urge, that of alimentation, is associated with the satisfying presence of a person, a relationship which is heightened if the child is breast-fed by a mother who is also in other ways the most important person in his life. For these reasons, it is easy to see how his mouth becomes a region of his body with somewhat specialized activities, capable of being highly charged with feeling.

The switch-over from what is primarily an in-taking activity to the out-putting activity of speech takes place during the second year. Nevertheless, speech does not begin with words, and for many weeks before he actually begins to talk, the child has started to babble in a purposive way, playing with his vocalization, and his cries have become distinguishable to those who look after him.

The significance of this can be seen in comparison with the repetitive, stereotyped often incessant cry of a low-grade defective child, or the occasional grunt or whimper of a more inert but retarded child who already in his crying "speech" fails to differentiate in expressing himself.

The rate at which speech develops is of course very variable but Gesell gives 8/12 as the average for the simple repeated syllable, such as "da-da" or "mu-mu", 14 months with an average of three words, two hundred words by 2 years, over eight hundred words by 3 years, and two thousand words at 5 years. We are thus observing a process of maturation, which is exceedingly rapid, and all the time expanding in many directions. Thus beginning with nouns, the child decorates his speech with verbs and later pronouns, adverbs and so on, aiming all the time at a more precise tool with which to express his meaning.

In the early experimental stages there is a good deal of trial and error, and the amount of available language is often neither full nor flexible enough to express all that the child wants to say. This becomes one of the stages in which a stammer may develop—out of the situation in which the child has a greater ideation than can be packed into his flow of words. The flow may, however, become even more jammed up if a parental demand adds tension, by bringing the imperfection of the whole process into evidence. We so often warn a child to "speak slowly" or to think what he is saying, when our instruction should really be to say what he is thinking, and better still, no instruction at all.

Speech, at this stage, is something with which the child asserts himself. If he feels that he will perhaps not be accepted (which may well be the case if he is talking too much or talking nonsense), he may try to withdraw, after the flow of speech has started, and hence comes the stopping and starting which appears to predispose to one of the many kinds of stammer.

In asserting himself, however, the child is also making a communication so that his speech involves him in a social relationship, although children will also hold long monologues in relation to their play activities, a kind of thinking aloud in coherent free-association.

Thus from the stage where he babbles, and then asserts himself, he progresses to where he talks to himself about his play (essentially an autistic activity) and from there proceeds to talking to someone, usually at first his mother, who, from his earlier experiences, he knows is certain to accept him. His speech has thus become an instrument of dual purpose, used for communicating his thoughts and feelings, and to establish a relationship. The two are interdependent, for communication implies a recipient, and receiving communication implies a relationship.

It is at this point that some children appear to break down, and I would like to draw attention here to the frequent involvement of speech as a symptom of serious maladjustment in children.

The fact that mutism, or all but that, occurs not uncommonly in children at once raises the question of psychopathology. Has this symptom a dynamic meaning? Is there any organic pathology? Is it a degenerative process, or a type of "disuse-atrophy" affecting a more recently acquired and more highly differentiated activity?

Certainly the child who ceases to speak is closing one of the most important doors on his own development. The reasons for this are obvious. He cuts himself off socially from contact with others, whether the care and attention of his elders, or the stimulation of his coevals in play. He will tend to arrest the development of his own language capacity as a whole. Not only will speech come less easily to him, but reading and writing will begin to suffer. The repercussions of these two will tend to a progressive withdrawal into himself. In other words, he becomes increasingly autistic, living, as they say, in a world of his own, eventually no longer seeking outside contacts.

In describing it in this way, I fully realize I may be putting the cart before the horse: the child may not so much withdraw from society as be driven into himself through lack of the common implements of social living.

The ease with which such a withdrawal can occur (for varying reasons) is illustrated by three cases taken from the records of children attending the Hospital for Sick Children, Great Ormond Street.

John (born 1.5.39).—Admitted with Tb. meningitis, April 1947 and hospitalized for 10/12.

Onset.—History of three weeks of headaches, getting worse with vomiting three to four times daily. For three days before admission was twitching and delirious.

Progress.—Comatose for 2/12. Papilloedema for 2/12, as he began to recover, speech was at first normal, then for one week stated to have a sensory aphasia, and a left-sided ptosis developed, but both recovered. Pupils remained unequal, Right > Left.

Family background.—Father killed in war. He had a pleural effusion earlier in life. Mother healthy. Patient youngest of three. Early history uneventful. Normal early development and an intelligent boy. He hardly knew his father and mother thinks she spoiled him on that account. He was fond of school and had the reputation of being a restless, mischievous youngster. As the mother had to work the maternal grandmother was mostly in charge of him.

He was referred to us for what was called "impossible" behaviour. He was difficult, sometimes destructive on the ward, and at a convalescent home he was spoken of as a kleptomaniac and found to be uncontrollable, perhaps because he was so inattentive to what was said to him.

His *deafness* was not noticed until he was faced with a routine intelligence test, although his mother suspected it when he was first home. It was confirmed by audiometer test and appeared to be due to a toxic neuritis.

His *speech* was unclear, poorly articulated, sometimes hardly intelligible. Although he used certain expressions suggesting intelligence, e.g. when a car outside backfired, he said "That's somebody letting off crackers", and another time he remarked "I must have a pair of new glasses", his speech besides being poorly articulated showed traces of his earlier aphasia.

He perseverated: for example, when he saw the sand tray he began to talk of seaside at Southend, when in fact he had been at Bexhill. For the next three or four remarks he brought in the phrase "sand at Southend" sometimes inappropriately. He could write his name, but immediately after doing so, wrote "motor" across it on the same piece of paper, without any obvious connexion.

Once he had returned home, and later been appropriately placed in a school for deaf children, his abnormal behaviour ceased, and it became possible to disentangle the clinical picture of hearing loss threatening a loss of speech which may have been partly aphasic, but was more likely associated with the deafness, since it was his intonation and his diction which were mainly affected. He co-operated perfectly, within his limits, on all the tests given, and his behaviour remained normal and he is having the use of a hearing aid.

The rapid threat to speech in a boy of 9 years, by no means totally deaf, was very striking. He was referred entirely on account of his behaviour problem, which became less, without specific treatment, as soon as his hearing loss was recognized and due allowance made for it.

Bobby (born 30.4.35) was referred in March 1946 for a stammer dating from a bomb episode in 1944. The stammer was a severe blocking and accompanied by a head-shaking tic, at times quite violent and by spasmodic facial twitching and blepharospasm. When seen he looked very scared and was all but speechless.

The history of the actual onset of his speech difficulty is instructive. He is the youngest of seven children. The mother and two of the children, including Bobby, were indoors in a Morrison shelter when a near miss shook the house. I asked the mother how she had felt and she said: "I had a heart attack, of course. My face stiffened and I couldn't breathe." Bobby became acutely hysterical and remained completely mute for two hours, though he ran round and round the room and had to be restrained. Following this incident, he was immediately evacuated to a strict foster-mother in Wales, where there was a good deal of Welsh spoken. No treatment was instituted until six months later after he had returned to London.

His previous history was uneventful; within a family of moderately slow developers, his rate of progress called for no comment. His I.Q. was just below average.

It is interesting that in Wales he continued to speak very little and to "behave queerly", i.e. meaning to convey an account of all his odd movements, mannerisms, &c.

Six months' speech therapy after his return to London did not alter his condition, and, when first seen, he was failing badly in school and sometimes truanting. He would scream over minor upsets at home, was afraid of the dark, and avoided mixing with other children, even to the extent of refusing to go to the pictures unless his mother was with him.

Treatment was a lengthy affair, but it revealed two outstanding points. Firstly, he played with the idea of aggressively hurting others and seemed very uneasy when he did so, gradually allowing himself to become more fierce and more outspoken in his attitude.

His fears relating to his mother seemed to be that at the time of the incident she was dead or that she was dumb. This he re-enacted to some extent in his two hours' mutism. Secondly, his solitariness, which had always been noticeable, was made much worse by his speech difficulties. Since he retreated from active participation he never knew how he would speak, and so he adopted an attitude of withdrawal from every difficulty or dangerous situation. The behaviour was essentially an hysterical reaction to an acutely traumatic situation, made worse or at least perpetuated, by the over-hasty removal from his mother into an evacuation which strongly fostered isolation, even down to being in a strange place with a strange language.

Lavinia (born 3.5.42).—Seen when aged 6.

Complaint was that she refused to talk whenever strangers were present or even in school to teachers. Would talk at home but not readily, and preferred to use her younger sister, aged 3, to ask for things she wanted.

Family history was negative though the father had been regarded as suspicious of others until he had grown beyond his adolescent period. He is now a very good father to the children and spends a lot of time on them. Mother, cheerful, affectionate, somewhat hasty. The home circumstances were good, above the average, and there had been no previous illness. Child began school just under 5, but her refusal to talk was developing into an antagonism towards teachers, and to some extent also to other children. She showed absolutely no interest in learning, which was taught largely by play methods. Her appearance was normal and she was physically well developed. Her early milestones were well up to average and she was a contented baby.

Her interviews with me were completely negative and silent. She would occasionally play a little, if I went to another part of the room and did not look. She would smile and appear perfectly friendly but also unco-operative in any form of activity. Her younger sister was included on some interviews. The latter chatted merrily the whole time, though her speech was sufficiently unclear to amount almost to a speech defect—difficult to evaluate at that age. The younger child constantly stole the limelight, which however was not difficult with so passive a partner. When I saw her alone there was no verbal response and no play until I went to the other end of the room, but that there was some response to my being there was shown when, on one occasion, I left the room and the child thought I had gone away. I returned to find her weeping loudly and looking for her mother in the passage. Curious things happened: on one occasion she stood silent for twenty minutes in the playroom, doing nothing, while on another she screamed for her mother while in the lavatory, but when mother arrived, she fought to keep her out and locked the door. For this she was sent to bed, but while up there, slipped out and was found playing with other children.

There was thus a curious mixture of withdrawal and opposition, and negativism to an extent suggesting an early psychosis, coupled with many instances of normal behaviour.

A relationship developed very gradually in treatment sessions until she became able to play at hiding herself from me, and a mutual game was tried of the hide-the-thimble variety.

One day, still without my ever having heard her speak, and two months after she had been attending regularly once a week for treatment, she teased to get a drawing which I had done and had concealed. It was a struggle to get it: when she did so she suddenly shouted "nothing" and tore it up. Play continued silently and during it, by getting her to draw, it became clear that she had no understanding of written language, or, of course, of reading. I am not sure how far this was *post hoc*, how far *propter hoc*, but quite clearly it linked with her total rejection of language.

It would have been difficult to continue this sort of blind man's buff had there not been, all this time, a striking and steady improvement in her behaviour at home, in shops and trains when out with her mother, and in school. In fact her behaviour and apparently her relationships had become almost normal.

In the course of the mother's discussions with the social worker, there emerged a clear picture of the extent to which she had coerced both children. She had been both ashamed of Lavinia and angry at her behaviour and exceedingly anxious that there might have been "something wrong with her brain". This led to her keeping a cane, in a vain effort to control and make this child behave normally. As she got better, the mother once said, "I feel safer somehow". In spite of efforts to see him, the father never came to the clinic.

Recovery after 3 months' treatment was clinically complete, and she spoke normally, though still very little, with me, and quite normally elsewhere. Her "illness" appeared to be a defensive retreat. I surmise that it linked closely with jealousy of her more forthcoming sister, but at no stage could I achieve anything which might be called an interpretation of her symptoms to her, or an acceptance of such interpretation with insight. She appeared to accept them silently, and to be able to make use of them, since even without speech she was able to maintain a relationship. The associated inhibition of reading, or indeed of any comprehension of the functions of reading and writing, seemed to me of great interest in linking up language as a total activity, in-taking and out-going.

This conception, and this case in particular, links very closely with the observed behaviour of psychotic children, who learn to talk, and then regress, as if withdrawing from the possibility of any contact with people. Others fail to develop language beyond a very rudimentary stage, the stage I have called self-assertive. Language with them never reaches a level at which it can serve as a means of communicating.

It is tempting to think that there is an organic deteriorating process at work in the psychotic child, where the absence of speech is such a striking feature. So far, the concrete evidence that this is so is lacking. One is therefore thrown back on a realization of the extreme importance to children of their speech. The means by which normal speech is acquired and maintained are more clearly seen when events such as these interrupt or deflect the usual path, taken by so many in their stride.

Dr. Ralph Noble (Cambridge) said that the fact that so many adults requested treatment, even undergraduates, for speech disorders showed that they had not been given any adequate treatment early in life.

In dealing with the treatment of speech defects one found that team work was essential. There were so many psychological factors which had to be understood and therefore a

psychiatrist should see the patient and work in conjunction with the speech therapist. In the case of children much of the shyness which was responsible for their trouble could be overcome if they were given a period of two hours at the speech centre under the observation and care of a psychologist, the parents being absent during this period.

In general, treatment should be undertaken individually rather than collectively because the main need was to establish confidence in the patient and this could not be achieved satisfactorily unless an individual approach was made.

Miss Joan H. van Thal: With reference to nomenclature: The Terminology Committee of the College of Speech Therapists, in recommendations published in *Speech*, March 1947 (pp. 19–20), advocated that *aphasia* be reserved to signify "deprivation of the powers of speech . . . a disturbance of the thought-language processes". *Alalia* signifying "a state of speechlessness" can be applied to failure of development of language in childhood. "*Developmental dysphasia*" has fallen into disuse, here and in America. The American *Journal for Speech Disorders*, March 1947 (pp. 17–22), sets out principles of nomenclature for speech disorders on an ætiological basis; for example, the term *dyslalia* is reserved for articulatory defects of childhood (often accompanied by departures from grammatical and syntactical standards) of a psychogenic nature.

Dr. E. Stengel (Institute of Psychiatry, London), commenting on aphasia in childhood, pointed out that left-sided temporal lesions which in adults would produce receptive aphasia usually associated with logorrhœa, would in young children cause loss of speech impulses in addition to loss of understanding of spoken language. The clinical picture of the speech disorder in such cases has much in common with that of congenital auditory imperception. A similar speech disorder has been observed in adults where both temporal lobes were involved (Mingazzini). The prognosis of the temporal aphasia in children is poor, while aphasias due to pre-central lesions usually disappear in a short time. He could not associate himself with the doubts which had been expressed regarding the existence of the clinical condition described as congenital word deafness (auditory imperception). Such cases did occur although the origin of the disability was still obscure. Possibly it was in some cases due to temporal lesions which had occurred at birth or soon after.

Dr. Colin Edwards, referring to the group of children mentioned by Dr. Miller in whom there was dysarthria in the absence of evidence of any detectable neurological lesion elsewhere, said that several such cases had been investigated at the West End Hospital for Nervous Diseases and at the Moor House Residential School for children with speech disorders.

The evidence all pointed to the presence of a structural lesion which was an agenesis, and the picture was essentially one of pseudobulbar palsy, there being spasticity and greatly limited movement of the muscles supplied from the medulla oblongata and also, at times, of the facial muscles.

Section of Medicine

President—Sir ADOLPHE ABRAHAMS, O.B.E., M.A., M.D., F.R.C.P.

[*February* 28, 1950]

DISCUSSION ON SHORT-TERM FEVERS OF OBSCURE ORIGIN

Professor C. H. Stuart-Harris:

(1) *Febrile disorders in general practice.*—There are few accurate records of minor febrile disorders as seen in general practice but those obtained in the Wensleydale villages by Pickles may serve to orientate us. Pickles (1948) found that 4,855 cases of infective disease occurred among a community of 3,230 people over a period of fifteen years. The disease leading numerically was influenza (1,112 cases), next came diarrhœa and vomiting with 1,018 cases, and then a variety of states with 500 or less cases. Of these, measles, varicella, whooping-cough, mumps, rubella, herpes zoster and diphtheria claimed 1,683 cases in all, and hepatitis, lobar pneumonia and scarlet fever a further 280. The conditions which lie more definitely within this discussion in addition to influenza are febrile catarrh (407 cases), tonsillitis (289 cases), glandular fever (41 cases) and Bornholm disease or epidemic myalgia (25 cases). It is not unfair to group influenza, febrile catarrh and tonsillitis together and these comprise 1,808 cases or 37% of the total group of infections. Diarrhœa and vomiting may also fairly be considered febrile conditions of obscure origin and this group includes a further 20% of the total. The surprising fact that respiratory disorders of obscure origin caused nearly 40% of all infections in a rural population is supported by figures collected last year by Pemberton (1949). A survey of the work of 8 practitioners in a winter and also a summer week of 1947, in and near Sheffield, indicated that respiratory disease comprised 41% of complaints in the winter and 21% in the summer. This contrasted with the figures for acute specific fevers which comprised 4·6 and 4·8% of complaints respectively in the same weeks. Analysis of the respiratory illnesses indicates the overall numerical importance of influenza, bronchitis, coryza and diseases of the pharynx and tonsils. The winter period of the survey was actually coincident with the peak in influenza deaths for February 1947, and this was a season of influenza A, though the epidemic was only a very minor one.

(2) *Febrile disorders amongst nurses.*—In a recent survey of sickness amongst nurses in training school or in hospital over a three-year period (1943–1945) Court

(1949) indicated again the major importance of acute respiratory infections in the causation of ill-health among nurses. Such were responsible for 40% of all attacks of illness and for 30% of lost working days. Dysentery and gastro-enteritis, skin disorders, hand infections and injury together accounted for a further 19% of illnesses but each of these alone caused 6% or less of the total. Infectious fevers caused only 2·5% of all sickness in these nurses.

During 1949, Dr. Joan Walker observed a group of 400 nurses at the Leicester Royal Infirmary. She has kindly allowed me to quote her findings of the number of cases of minor febrile disorders in these girls. Of the 207 cases of illness diarrhœa and vomiting caused 45 (21%), and 143 of the rest of the cases (69%) comprised minor respiratory illnesses ranging from colds to influenza and atypical pneumonia. During March there was a small outbreak of influenza and Dr. Walker kindly submitted samples of serum from 14 cases to my laboratory. Ten of these gave serological proof of influenza virus infection, one was a case of influenza B and the rest were cases of influenza A. There is a reasonable presumption therefore that the separation of influenza from the rather varied pattern of respiratory illness was a valid one. Of the other diagnoses, tonsillitis with 49 cases probably included many streptococcal infections, but most of the other ones may reasonably be regarded as virus infections. The 6 cases of atypical pneumonia were of particular interest. One was undoubtedly associated with influenza A, but neither of the other 2 which were tested serologically was proved to be due to this agent.

In Sheffield during 1949, my colleagues Drs. P. W. W. Gifford and H. R. Worth have been in charge of the Health Service at the United Sheffield Hospitals. They saw 291 cases of illness among 462 nurses at the Royal Sheffield Infirmary and Hospital during the twelve months' period and, of these, upper respiratory infections totalled 73 and influenza 39 cases. The latter cases were grouped in March and April 1949 and in a number of those which were tested, evidence of influenza A was obtained either serologically or by isolation of virus from the throat. The incidence of these infections was thus lower than that in the nurses in Leicester, but comprised an important bulk of the total morbidity (38%). Diarrhœa and acute specific fevers, however, did not contribute a single case during the period of observation. The nurses at the special hospitals (Jessop and Children's) were only studied for six months but respiratory infections were prominent among nurses at the Children's Hospital, and less so at the Jessop Hospital for women.

(3) *Absenteeism in industry from short fevers.*—Industrial sickness records cannot really be compared with either of the preceding groups because they are largely based on certificates of illness sent in by practitioners. Nevertheless, such records as I have been able to inspect have indicated that diseases of the respiratory tract are major causes of absenteeism. The rates of sickness at the Boots group of factories at Nottingham are constantly under the survey of Dr. T. A. Lloyd Davies who finds that so-called infective diseases cause an annual absence-rate of 250 per thousand persons in men compared with a total absence-rate of 646 per thousand. For women, the figures are 559 per thousand out of a total rate of 1,412 per thousand. These figures were based on the period from July 1, 1948, to June 30, 1949. At a large steelworks at Sheffield, my colleague Dr. John Pemberton has carried out an analysis of cases certified as "Flu," influenza or coryza compared with the total sickness. The period of analysis was January to June 1949 which includes the months of March and April when influenza A caused a moderate outbreak of illness in Sheffield. It appears that this outbreak was responsible for half of the sickness in the workers from all causes in these months whereas the percentage fell to 8% in May and June when influenza had ceased to be prevalent.

Clinical Differentiation of Short-term Febrile Disorders of Obscure Origin

To the clinician, the minor respiratory disorders furnish an almost continuous range of clinical types—a spectrum as Dingle (1948) has called it—from the mildest cold to the most severe infection of the lower respiratory tract. Even the separation of that group of cases due to the operation of the influenza viruses has done little to help us clinically because of the frequent mimicking of such cases by other febrile conditions which fail to yield evidence of infection by these viruses. We cannot but recognize that we are in the earliest phases of recognition of distinct entities from the ætiological standpoint within a mixed hotch-potch of clinical states. Most of our diagnoses in this group tend to emphasize points of anatomical separation and we call this case pharyngitis, that one tonsillitis, a third laryngitis and a fourth bronchitis. The careful study which has been made in many countries of the one virus disorder of which we know reasonably the clinical boundaries of the infection in man—namely influenza—gives us a very different viewpoint. Entirely subclinical infections, minor one-day fevers with trivial symptomatology, so-called "typical" cases of three-day fever and cases with lower respiratory tract infection such as a bronchitis or a bronchiolitis can all be due to the same virus, unaided, so far as can be told, by bacteria. Until we know the full clinical pattern of the other acute virus infections of the respiratory tract as outlined by correlated studies of clinical states with precise laboratory evidence, it would be idle to speculate upon small clinical resemblances and differences. However, we can recognize at present four main syndromes of respiratory tract disease which call for differentiation in individual patients.

(1) *Clinical influenza.*—By this we mean a short febrile clinical state with sudden onset and constitutional symptoms of headache, malaise, prostration and muscular pains and relatively minor evidence of respiratory tract involvement. Such is the average or "typical" clinical case of infection by either of the influenza viruses as seen during epidemics, and the diagnostic problem at such times is not too formidable. Yet sporadic cases conforming to this definition occur all the year round, though not in large numbers, and even in years when there are no epidemics. At such times it seems clear that the infection is frequently due to sóme agent other than that of the influenza virus which we can identify by ferret or egg inoculation or by serological tests. The agent responsible for acute respiratory disease or febrile catarrh can certainly cause a picture identical with that associated with the influenza viruses at times though it is questionable whether this is, in fact, its normal or average pattern. Of course very many other disorders can cause a similar attack including mild typhus, sandfly fever, streptococcal pharyngitis and many others. Pyelitis is certainly an important differential diagnosis particularly in women and all clinicians could contribute from their experience to the list of possible causes. But the frequent accompaniments of widespread influenza virus infection in the community are characteristic and include a rise in deaths of an acute character from respiratory and indeed all causes, and an increase in cases of pneumonia.

(2) *Febrile catarrh.*—This is a condition of less acute onset than clinical influenza with emphasis upon respiratory tract rather than constitutional symptoms. After a cold or sore throat for two or three days there is an unproductive cough and the temperature then rises but the sufferer is often more concerned about his nasal cold or his throat than about his headache. Nevertheless, I admit that it is not true that prominence of respiratory tract symptoms should be taken as in any way ruling out a diagnosis of influenza. The mixture of clinical types within a group of those smitten by febrile catarrh is, however, a most useful pointer and especial emphasis must be placed on the occurrence of a faucial exudate in catarrhal states which is only seen exceptionally in influenza. Exudate tends to suggest the hæmolytic streptococcus

but infection of the throat by the latter produces a follicular or confluent white membrane. The exudate of febrile catarrh is a glairy or mucopurulent secretion often diffusely coating the tonsils and adenoid tissue. Cervical adenitis is not prominent. Dingle and his co-workers (Commission on Acute Respiratory Diseases, 1947) have separated off the group of cases with exudate as "non-streptococcal exudative pharyngitis", but there is no knowledge as to whether such cases are ætiologically distinct from the non-exudative cases of febrile catarrh. The latter, by the way, often take the form of a rather severe laryngitis or tracheitis and I have been impressed by the frequent severity of febrile catarrh in individual cases which may exceed that seen in influenza. Cases with bronchial involvement have certainly occurred in the past but I am no longer sure that such are not cases of atypical pneumonia which tend, in any case, to be mixed up within the group of cases of febrile catarrh.

(3) *Atypical pneumonia.*—Involvement of the lower respiratory tract with signs of bronchitis rather than consolidation, absence of leukocytosis, and a radiological pattern with diffuse homogeneous or perivascular change indicate that one may be dealing with an atypical pneumonia. The onset is essentially insidious, but headache and shivering accompany the fever and so also do the symptoms of respiratory tract involvement and particularly frequent cough and mucoid or mucopurulent sputum. In view of the more prolonged fever which lasts seven to fourteen days or more it is doubtful whether atypical pneumonia should be included in the group of conditions under discussion or not. However, in its early days, it constitutes a most important differential diagnosis both of influenza and of febrile catarrh. Nor can we neglect the fact that many authorities believe that non-pneumonic cases with minor respiratory illness occur frequently. If it were not for the cold agglutinins in the serum during the second week, it would be difficult to particularize ætiological groups within the atypical pneumonias. However the cold agglutinin response is not usually seen in the cases of atypical pneumonia due to Q fever rickettsiæ or in those due to viruses of the psittacosis group. Until research has outlined a virus agent which can be linked with cases of atypical pneumonia associated with the cold agglutinin response, we shall remain in doubt concerning the clinical limits of what is probably the commonest variety of atypical pneumonia in this country.

(4) *The common cold* is usually an afebrile disease. However, febrile colds do occur and I have often wondered about that variety of clinical case which begins with fever as in influenza, but which is followed after subsidence of fever by violent outpourings of nasal secretion closely resembling an ordinary cold. I do not associate such a clinical pattern with influenza virus infection at all commonly.

(5) *Other febrile states of obscure origin.*—Epidemic gastro-enteritis or D. and V. means, to some people, gastric "flu" but I have seen no evidence in the past fifteen years which justifies this appellation. There is, of course, the occasional occurrence of abdominal pain or vomiting particularly in the earliest stages of influenza but the relatively sudden onset of diarrhœa and vomiting perhaps accompanied by fever and often seen in the form of explosive outbreaks has never, in my experience, proved to be due to infection with an influenza virus. In addition to the outbreaks proved to be due to Sonne or Flexner types of dysentery bacilli, there is the variety unassociated with any of the dysentery or salmonella organisms and which may be due to a virus agent. Workers in America (Reimann *et al.*, 1945; Gordon *et al.*, 1947) claim that proof has been obtained that filtrates of stools of sufferers from this condition will infect human volunteers either by inhalation or by oral ingestion.

The myalgias include Bornholm disease and abortive poliomyelitis. Though isolated cases might be confused with influenza, the occurrence of abdominal and later shoulder-tip pain in Bornholm disease, and the stiff neck or back accompanying the muscular pains of abortive poliomyelitis, should point to the diagnosis.

Finally, glandular fever does not properly lie within my field of discussion and I only mention it because it seems so often to be a puzzling disease to diagnose. There is enough variation in the clinical picture of cases with definite glandular enlargement to make it impossible for us to be certain of other milder cases. Indeed the full delineation of the clinical pattern of any infectious disease can only be made when the ætiological agent is defined or else a specific serological test based upon the agent has become available. Until then, we shall continue to be puzzled by differentiation on the one hand from rubella and infective hepatitis and on the other from conditions associated with lymph-gland or splenic enlargement. Moreover, the blood count in cases which show no marked mononucleosis is often bewildering.

In conclusion, it seems to me that the need to-day is for a general recognition of the importance both numerically and from the economic standpoint of the minor febrile disorders of the respiratory tract which have hitherto failed to interest largely because of the absence of clear-cut differential points. Acute respiratory disease due to one or other of the groups of viruses which have developed the facility to attack much the same zone of the human respiratory tract indeed constitutes a major unsolved problem in the shrinking field of infective disease and particularly in those infections for which we lack either effective methods of therapeusis or of prophylaxis.

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Dr. C. J. Gavey: *Obscure short-term fevers in hot countries.*—During war service in the Middle East I interested myself in obscure fevers of short duration and made some clinical observations. The term P.U.O. (pyrexia of unknown origin) is used for brevity.

Incidence.—When drafted overseas our difficulty was to acquire some useful guidance as to the incidence of P.U.O., and indeed of the incidence of common specific fevers, in hot countries. Tropical medicine differs considerably from area to area and its textbooks suffer even more than usual from unduly comprehensive descriptions of disease, as opposed to individual examples, here specially connected with location. The history of the first World War contained little information on P.U.O. except in regard to sandfly fever and dengue fever. Bulmer (1943) first gave us an idea of the magnitude of the problem of P.U.O. so far as the Middle East was concerned. Short-term fevers accounted for 15% of a series of 13,542 Military Hospital cases, whereas in India Leishman and Kelsall (1944) gave a percentage of 9·7 in 11,645 cases. When official statistics became available it was confirmed that P.U.O. was as common as malaria in many parts, and I was able to prove this for myself on several occasions in Egypt, Palestine and Malta. I now give an example.

I chose two wards with a total of 96 beds and admitted to them 122 medical patients in one month, excluding only cases of dysentery and tonsillitis. Malaria was, of course, endemic though the area immediately surrounding the hospital was not malarial. Infective hepatitis was not prevalent at the time. A standard clinical analysis sheet was used to ensure that no important feature of each case would be overlooked. An *aide-mémoire* (shown in Table I) was prepared. Table II shows the closely similar

TABLE I.—AIDE MÉMOIRE FOR OBSCURE FEVERS

Malaria	Bacterial endocarditis	Boils
Enteric	Atypical pneumonia	Sinusitis
Amœbiasis	Tuberculosis	Stomatitis
Undulant fever	Glandular fever	Cholecystitis
Sandfly fever	Infective hepatitis	Urinary infections
Relapsing fever	Choriomeningitis	Perinephric abscess
Typhus	Weil's disease	Subphrenic abscess
Kala-azar	Syphilis	Pyosalpinx
Ancylostomiasis	Psittacosis	Septicæmia
Bilharzia	Rat-bite fever	Inoculations
Filaria	Diphtheria	Allergy
Ascaris lumbricoides		
Trichinella spiralis	Hodgkin's disease	Sunburn
Actinomycosis, &c.	Leukæmia	Heat exhaustion
Tropical thrombophlebitis	Neoplasms	Unstable heat-regulation centre. Goitre

TABLE II.—TOTAL ADMISSIONS: 122

June. 96 beds

A. *Febrile Diseases*		B. *Non-febrile Diseases*	
P.U.O.	30	Fibrositis	4
Malaria	31	Anxiety state	3
Upper respiratory infection	14	Dyspepsia	2
Bronchitis	7	Emphysema	2
Pneumonia	7	Helminthiasis	2
Diarrhœa	5	No disease found	2
Boils, &c.	3	Albuminuria	1
Tuberculosis	1	Cholecystitis	1
Infective hepatitis	1	Facial palsy	1
Inoculation effects	1	Hepato-splenomegaly	1
Dental abscess	1	Nystagmus, NYD*	1
		Osteoarthritis	1
	101		21

Incidence of P.U.O. 24·6%.

*Not yet diagnosed.

incidence of P.U.O. and malaria and it should be noted that the diagnosis of P.U.O. was made reluctantly after failure to class each case in one of the categories shown in Table III. Clinical malaria, upper respiratory infections and sandfly fever were the commonest fevers in the differential diagnosis.

TABLE III.—DISEASES MOST CLOSELY SIMULATED BY DISEASES CLASSED AS P.U.O.

No. of cases: 30

Malarial clinical	11	Staphylococcal bacteriæmia	1
Upper respiratory infection	6	Amœbic hepatitis	1
Sandfly fever	5	Undulant fever	1
Pneumonia atypical	1	Typhus	1
Skin infection	1	Enteric clinical	1
Inoculation effect	1		

CLINICAL FEATURES

The great majority (26 of 30) of fevers of obscure origin were short-term and they were scarcely more disabling than influenza in this country. They all presented in much the same way as expected when fever is dominant. Headache, eye ache, stiff neck, limb pains, and backache, anorexia, constipation or diarrhœa, respiratory catarrh, occur in more or less degree in all fevers. Scott and Warin (1946), working in Cairo, showed that headache, which they studied specially, differed little in sandfly fever, malaria, typhoid, dysentery, or pneumonia, pneumococcal or atypical. Nevertheless the various fevers can often be distinguished by the mode of onset, by the prominence of certain of the symptoms and signs, and by awareness of the prevalent infections.

Duration of fever.—I adopted the principle that this should be measured from the onset of *symptoms* to the end of the febrile period, e.g. two days' symptoms before reporting, or admission, and three days' subsequent fever, totalling five days. The average in the small series mentioned, which was representative of many other groups of patients studied, was 3·6 days (1·2 + 2·4). This period is short and reminds us of the relatively benign nature of the illness. In view of the miscellany of conditions included in P.U.O. discussion is facilitated by subdivision as in Table IV. An example

TABLE IV.—CLASSIFICATION OF P.U.O.

Place where treated: Egypt.		
Patient's country of origin: UK—20. Non-UK—10.		
Short term 1–7 days.		
Designated e.g. 2+4=6, i.e. 2 days' symptoms before admission and 4 days' fever after admission		26
Long term 8–28 days.		
Continued	1	
Recurrent	1	
Recrudescent	2	4
Protracted over 28 days.		
Continued, recurrent or recrudescent		0
Splenomegaly: Transient under 7 days	3	
Persistent over 7 days	2	5
White cells: Normal 5,000–10,000	10	
Leukopenia under 5,000	2	
Leukocytosis over 10,000	5	17

of a full diagnosis is: P.U.O. Short-term. 2 + 3 = 5 days. No splenomegaly, Leukopenia. British, United Kingdom (U.K.) in Egypt.

Important *physical signs* are often transient. The rash of typhus, for example, was noted on the sixth day only, in one case. In atypical pneumonia localized crepitations may rapidly vanish though diminished movement on the affected side is more lasting and lung shadows confirm when X-rays are not too long delayed. The spleen and liver are frequently reported to be enlarged when, in fact, they are not. If a spleen is palpable it should be possible to confirm the sign repeatedly at the same examination. Ordinary palpation is not likely to cause the spleen to contract. If it is felt only in the lateral position this should be stated. It does seem very desirable to differentiate P.U.O. with splenomegaly from that without (Table IV). Liver enlargement is a sign of great interest in the tropics. One becomes adept at palpation and a barely palpable liver margin need not be significant, yet one must not miss infective hepatitis or amœbic hepatitis for want of respect for it.

FEVERS OF SPECIAL INTEREST

Malaria is the great mimic: Hunt (1944) says: "Diarrhœa with blood and fever is not always due to dysentery; jaundice with fever is not always infective hepatitis: malaria may mimic both. Asthma, fibrositis, neuritis, urticaria, and nephritis are only some of the less well-recognized conditions that malaria may cause, while it may simulate a dozen others."

Infective hepatitis may show little jaundice yet violent symptoms, even meningism or a small patch of pneumonitis, may be seen. Jaundice may appear late.

Glandular fever is endemic almost everywhere and small groups of cases may be atypical in their presentation. A group of 8 sailors sleeping on the same deck were all infected. This condition is often responsible for symptoms like the effort syndrome, but careful search for glands may lead to the correct diagnosis. I remember one patient who had only one small pectoral gland to suggest the disease later proved by blood examination.

Poliomyelitis may present as a P.U.O. till paralyses appear within a few days, though there are cases in which the paralyses become apparent when the illness is over. A good example is shoulder-girdle palsy.

Atypical pneumonia must always be remembered and if suspected early a transient X-ray shadow may clinch the diagnosis. Undoubtedly we missed many such cases during the war.

Choriomeningitis is prevalent in hot countries and intense headache with little fever may lead to a lumbar puncture with characteristic findings.

Fever in *smallpox contacts.* Howat and Arnott (1944) reported an interesting pneumonitis in staff attending smallpox cases. Chest signs were not prominent but X-rays revealed mottling at the lung bases. Fever lasting up to twelve days varied from 100–104° F. There were no untoward sequelæ.

Thrombophlebitis.—Cases of unexplained thrombophlebitis occur in the tropics, epidemic (Manson-Bahr and Charters, 1946) or sporadic. Our interest in the condition lies in the short-term fever which is liable to relapse and the thrombophlebitis may be easily overlooked. A virus infection is postulated owing to the relative lymphocytosis. Fortunately embolism is extremely rare.

Filariasis is an important cause of obscure fever. Its manifestation may be delayed for many years, 20 in a patient I saw. There is now considerable prospect of success in treatment from a new drug Hetrazan (1-diethyl carbamyl-4-methyl piperazine) reported in America in 1947 (Santiago-Stevenson *et al*). The drug has the advantage of oral administration.

Epidemic epididymo-orchitis (Tunbridge and Gavey, 1946) as seen in Malta was characterized by a short prodromal fever, an apyrexial interval of a few days, followed by a second, testicular fever. This testicular fever was accompanied by unilateral swelling which subsided considerably during the first week, but might take a month to clear completely. There was no evidence of urinary infection and we could not incriminate any of the fevers which may be complicated by epididymo-orchitis, e.g. sandfly fever, undulant fever, mumps, malaria, filariasis, enteric fever, chorio-meningitis, meningococcal meningitis, glandular fever, and atypical pneumonia.

Sandfly fever.—Doubt has often arisen as to whether this is an entity to be differentiated from other short-term fevers. Certainly fevers were extremely frequent during the sandfly season from May to September and some 1,000 cases might be admitted to a large military hospital in one season. The severity varied much and apparently the Indian was less severe than the Middle East type. There was a definite tendency to relapse. A few patients suffered from meningism and prostration but on the whole recovery was speedy and comparable with influenza or febrile catarrh. The pulse was not remarkable and a tendency to bradycardia could be explained by the fact that many young men have normally a slow pulse. Leukopenia was common. During epidemics the term sandfly should be retained, for it serves to narrow the comprehensive group of short-term P.U.O.s which, though self-limited and not fatal, are responsible for much loss of time.

Dengue fever caused by a mosquito, *Aëdes ægypti*, was not seen in the Middle East and I have no experience of it, but it was common in India. There is a characteristic rash in about 70% of cases and relapses are more frequent than in sandfly fever. Both sandfly fever and dengue have a sudden onset with high fever. Rigors may occur but are not as severe as in malaria. The spleen is not enlarged. Catarrh is not prominent unless the patient already has a chronic upper respiratory infection. Diarrhœa may occur in patients prone to gastro-intestinal disturbance. The face may appear congested as in other virus diseases.

Tonsillitis should be mentioned because patients may not complain of sore throat yet this may be an adequate explanation of a short fever.

Skin infections are so common in hot countries that patients do not readily draw attention to them. The perineum is specially liable to be overlooked.

Septicæmia due to staphylococcal skin lesions is commoner in hot than in temperate climates and osteomyelitis of the spine is a favourite pyæmic manifestation.

Epidemiology

Whenever one is faced with an epidemic or an outbreak of a fever there will be numerous abortive or atypical cases, and in order to round up these the following classification is necessary. For example, in typhoid five categories are possible, i.e. (1) typhoid, (2) enteric clinical, (3) P.U.O. enteric contact, (4) enteric contact without fever, (5) P.U.O. During the epidemic of typhoid in Malta we were faced with a number of patients classed as P.U.O.s whose spleens were palpable and upon review we had no doubt that some at least of these were abortive typhoid and should have been included in the total. When it is reasonably certain that a P.U.O. is, in fact, a specific fever incapable of proof, e.g. typhoid met after a febrile phase, or undulant fever with negative agglutination tests and negative culture, the term clinical enteric or clinical undulant fever should be used. This classification enables a complete study of borderline cases which can be traced and were this system accurately pursued there would be fewer cases of P.U.O. A continual awareness of endemic or epidemic diseases is essential, or cases may be missed in the absence of an epidemic.

Laboratory Investigation

In dealing with short-term P.U.O. familiarity tends to breed contempt yet very grave diseases such as enteric may masquerade under that diagnosis; but apart from blood slides for malaria in all cases and particularly when malignant malaria is prevalent, and a white cell count if fever persists more than a few days, one need not rush to elaborate investigations. The first assessment of any patient is usually the most important and accurate clinical study guides us faithfully to the proper initial investigations. But if by the seventh day of the disease a diagnosis has not been arrived at, then the matter is serious and demands careful review of all the features of the case; for if the fever does not prove fatal, as might happen in enteric fever, considerable invalidism is likely. There is no doubt that much time spent in laboratories on the investigation of short-term fevers could be used more profitably in the study of fevers of longer duration. In addition to blood films, counts and cultures, sternal marrow cultures, stool and urine microscopy and culture, agglutination reactions, search for tubercle in any system, prostatic smears, cerebrospinal fluid examination, animal inoculations, and X-rays, may all be useful. The Kahn reaction may give false positives and the reactions should always be repeated when fever is over.

Recurrent Fevers

A patient may have a short P.U.O. and be considered fit for discharge when fever recurs and perhaps a severe typhoid relapse is beginning. Such cases are disquieting but are fortunately uncommon and if the patient is carefully interrogated on discharge such errors should rarely happen. During an epidemic of infective hepatitis it is not practical to keep all patients with short-term P.U.O. in hospital until the limit of latency of jaundice is reached. It is wise, however, to warn the patient to see his doctor after discharge if his appetite fails; the urine may then show a trace of bile. The limit of latency of jaundice is probably fourteen days after the initial symptom, but the average is three to seven days. For typhoid the interval between fevers is on the average four days but the limit is three weeks. Choriomeningitis, atypical pneumonia, and relapsing fever are other examples of recurrent fevers with a considerable afebrile interval.

Treatment

Knowing that many of these short-term P.U.O.s are likely to be of virus origin, should we use antibiotics such as aureomycin that are known to have a noxious effect on viruses? I contend that as the bulk of the P.U.O.s are self-limited, powerful remedies should not be readily exhibited, for there is a great tendency to allow them to supplant adequate rest, hence the frequency of the post-infective effort syndrome. Moreover, such so-called specific remedies may fail in actual practice. In this connexion I mention an epidemic of sore throat in a group of 72 A.T.S. who ate infected cheese. The organism, a streptococcus, was sulphonamide sensitive, and some were treated with this drug and others not. There was no difference in the rate of resolution even though the drug was given within twenty-four hours of the onset of the illness. Aspirin and tab. codeine co. are very valuable analgesics and should never be withheld for fear of masking the diagnosis.

There is considerable danger that influenza may be treated with new antibiotics whose effect will take a long time to evaluate, and we should therefore remember the aphorism, *primum non nocere*—first do no harm.

I am much indebted to the Director, Army Medical Services for permission to publish this report which is based on experience gained during the late war.

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Section of Anæsthetics

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DISCUSSION ON MUSCULAR RELAXATION IN ABDOMINAL SURGERY

Mr. Rodney Maingot (*Surgeon to the Royal Free Hospital, London*): I am here to recount to you my experiences of "tight belly" as I have encountered it during the performance of abdominal operations; to discuss the ætiology of the condition; to consider the serious, strange and diverse effects "rigidity" may have on the patient, on the anæsthetist and on the surgeon alike; and to record the methods employed by the anæsthetists with whom I have worked to combat and to reduce the incidence of this troublesome "complication".

(A) GENERAL CONSIDERATIONS

(1) It is unwise to adhere to a fixed routine in the selection of anæsthesia for abdominal operations; no hard and fast rules can be made.

(2) In unskilled hands the anæsthetic risk to the average patient is as great as the surgical risk.

(3) The agents and techniques employed at the present time for producing anæsthesia are of little consequence as compared with the ability of the anæsthetist. There are, in fact, no safe anæsthetic agents and no safe procedures in the hands of the occasional anæsthetist.

(4) Satisfactory muscular relaxation is the supreme and the most pressing demand of the anæsthetist. As the anæsthetist has to contend with so many variables, the ideal state of profound muscular relaxation may be difficult or even impossible to achieve in certain recalcitrant patients. We would all agree with Lundy that no known agent, no combination of drugs, and no type of "balanced anæsthesia" is guaranteed to produce maximal relaxation *in all patients*, who may differ widely in their response to various anæsthetic drugs and even to the same drugs at different times and under different circumstances.

(5) Some surgeons prefer one type of anæsthetic to another. This preference is usually based upon prejudice rather than upon scientific fact.

(6) Some surgeons prefer certain anæsthetists to others. Many factors may influence this preference: confidence; experience; loyalty, friendship and trust cemented by hospital or other associations; and the accepted benefits and excellent results which accrue when two experts, who have co-operated for many years, have mastered their individual techniques and work together as a harmonious team. Surely, for most anæsthetic and surgical procedures technical skill is all that is required to secure satisfactory results.

(7) The *agent* and *method* selected should be chosen not on a basis of the preference of either the surgeon or the anæsthetist, but because certain indications or contra-indications are present. The patient's recovery should be the first consideration; the surgeon's whims may come second. To-day the master word in anæsthesia is safety. The safe anæsthetist

does not necessarily belong to any one school of thought or cult, nor is he wedded to a sequence. He should not be catholic or conservative in his choice of drug, nor should he subjugate himself to the routine use of ether, spinals, blocks, barbiturates or curare. The ideal anæsthetist must be "flexible"; in other words, whilst adhering to certain principles, he must wisely select and employ the agent and method which he deems will best meet the special requirements of the particular case, and at the same time be prepared to placate a stubborn operator or to accept with a modest nod and an encouraging smile the hearty approval of a wise surgeon.

(8) There is a definite morbidity rate and mortality rate following operations on the "tight belly". The morbidity rate and the death-rate among surgeons who have consistently to operate under adverse conditions have never been accurately assessed!

(9) During the conduct of an abdominal operation the surgeon can do much to reduce the anæsthetic load. Incisions should be well placed and of ample proportions, and should in addition afford direct approach to the organ or organs to be investigated. The necessity for gentleness and for control of hæmorrhage needs no comment. Surgeons owe a great debt of gratitude to anæsthetists in that they have made possible many of the important advances in surgery. Without modern expert anæsthesia and replacement therapy, the majority of radical and time-consuming operations could not be carried out in a safe or satisfactory manner.

Anæsthesia is a difficult and expanding study. The modern anæsthetist is an all-rounder —physician, cardiologist, bronchoscopist, research worker in drugs and complex machines, an expert in intravenous therapy and in diagnostic and therapeutic blocks, and a therapist for the relief of pain. In the future he will be called upon to take a greater part in clinical work and also in the pre- and post-operative management of patients.

Anæsthetists have, in my opinion, been slow to insist upon the urgent necessity of having *regular out-patient sessions for anæsthetists*, where certain types of patients may be referred to them days or weeks before operation rather than on the eve of what may be—and often is—the biggest event in a man's life. The lack of a *post-anæsthesia room* in most general hospitals is also to be deplored. The recovery period is not without its well-known dangers, and a number of unconscious and unco-operative patients following a heavy operating list throws an insurmountable burden upon the nursing staffs in the wards. The post-anæsthesia room should be large, comfortable and warm, and should contain all conceivable facilities for resuscitation. It should be staffed by a resident anæsthetist and a surgical registrar, and by nurses specially trained in modern methods of post-operative therapy. I would urge the adoption of this plan which has proved so successful and indispensable in those hospitals where it has been given a fair trial.

The Tight Belly

The opposite of the much-desired muscular relaxation which we are discussing is colloquially known as the "tight belly".

The effects of the tight belly are widespread, as they involve the patient (the most important person present at an operation), the anæsthetist, the surgeon, the assistants, the sister, the nursing staff, the porters, the students and the visitors to the operating room.

"Tight abdomen" affects the *patient* adversely. It increases shock, raises the morbidity and mortality rates, encourages hæmorrhage, thrombosis, ileus, chest complications and infections of the wound, is associated with a high incidence of burst abdomen and incisional hernia, and militates against the performance of a carefully planned atraumatic procedure.

The immediate repercussions of the tight belly upon the *anæsthetist* are varied and interesting. He may be flustered or register excitement, but as a rule character and training tell in the long run. He is, as you know, usually aloof, cool and collected—master of the situation.

The sequence is often this: he will give an injection into the arm, using some type of curarizing agent; he will adjust various tubes, taps and bags, or multicoloured cylinders; and then, following a variable period, a placid smile will light his face and he will say quietly and as pleasantly as he can—"How is he now?"

The effects on the *surgeon* of muscular rigidity during the conduct of an abdominal operation are quite unpredictable, although often dramatic. It is usually a test of a man's character. The most quiet, peaceful, unassuming surgeon may in an instant be transformed into a raving, gesticulating, shouting, threatening monster, with hate in his eyes. On the other hand, he may affect indifference and whistle—something frivolous if the abdomen is not too tight and hope not too long deferred; but if he is in a facetious mood and the belly is obstinately

unyielding it may well be "Coronach". There are others who keep their equanimity at all times and remain unruffled and untrammelled in the moments of great stress and in the face of such happenings. Some surgeons, again, bide their time, and after placing a large swab over the offending muscles to hide them, remain mute; but should speech come at such a time as this, it is not in measured tones about the advent of Spring, but rather about the devastating effects of the H-bomb.

(B) Special Considerations

(1) *The choice of anæsthesia.*—The choice of agent and the method of administration for anæsthesia in abdominal surgery are largely dependent upon the following: (*a*) The age and physical condition of the patient; (*b*) the type and site of the disease; (*c*) the extent of the contemplated surgical procedure, including the time factor; (*d*) the anæsthetist; (*e*) the surgeon; (*f*) the facilities which are available.

(2) *The methods of obtaining muscular relaxation.*—(*a*) Deep general anæsthesia by depressing the central nervous system; (*b*) blocking nerve roots by spinal or epidural block; (*c*) intercostal block or field block—with or without splanchnic block; (*d*) myoneural block by curare or a curare-like agent.

(3) *Advantages and disadvantages of the agents and methods employed.*—(*a*) *Pentothal-gas-oxygen-ether:* This sequence is a good example of "balanced anæsthesia" and is deservedly popular, as ether is well tolerated by most patients. The method has a wide margin of safety when given with a high concentration of oxygen; muscular relaxation is good; and breathing is quiet. Ether is employed for a large number of abdominal operations and is the drug of choice—or at least it should be—for the occasional anæsthetist. It is specially indicated for operations in infancy and childhood; for good-risk patients who are not unduly muscular; and in cardiac patients who cannot tolerate a fall in blood pressure.

Unfortunately ether has many well-recognized disadvantages and contra-indications. It is often concerned in the ætiology of "tight belly", particularly when administered to those who are powerfully built, strong, or obese; it is sluggish and unreliable in its action in cases of peritonitis; it increases the incidence of vomiting and pulmonary complications following radical, time-consuming procedures; it has undesirable curariform properties; and it is dangerous when employed in cases of hepatic and renal insufficiency and in diabetics.

(*b*) *Pentothal and pentothal-gas-oxygen:* Intravenous pentothal *alone* has been used for short operations such as appendicectomy and in thin and asthenic patients. Pentothal, whether used alone or (preferably) accompanied by gas and oxygen, does not produce satisfactory muscular relaxation of the abdominal muscles. As an agent for producing rapid, pleasant and peaceful amnesia it stands unrivalled. It is well-nigh impossible to assess beforehand how much pentothal will be required to produce the optimal level of anæsthesia for a particular patient. Therefore the safest way of doing this is by small and slowly administered doses. Many of its advantages are lost when it is used for abdominal operations requiring the injection of large doses. These large doses in turn cause the patient to sleep for hours and predispose to hypoxia, respiratory depression and chest complications. The first principle in the use of pentothal, as well as in general anæsthesia, is the maintenance of a free and unrestricted airway, as most of the contra-indications and complications centre around this factor.

The chief contra-indications to pentothal are shock, debility, old age, toxæmia, oral and pharyngeal sepsis, and renal and hepatic failure.

(*c*) *Cyclopropane:* Cyclopropane anæsthesia should be reserved solely for the expert. When skilfully used it produces quiet breathing and less pulmonary complications than ether. It does not, however, produce sufficient muscular relaxation to satisfy the fastidious abdominal surgeon; hence it is most frequently combined with minimal ether, regional or intercostal block, or curare. The combination of cyclopropane-curare finds its most useful application in operations for acute perforated peptic ulcer and has been in a measure instrumental in reducing the mortality in this grave catastrophe from 20% to about 5%.

(*d*) *Spinal Block:* In my opinion spinal block supplemented with light intravenous or inhalation anæsthesia provides the surgeon with operating conditions which closely approximate the ideal. High spinal is especially indicated in fit, sthenic, muscular patients. The quiet regular action of the diaphragm, the contraction of the intestines and the complete relaxation of the abdominal muscles produce a happy surgeon.

The agent and method to be employed in spinal analgesia depend upon the contemplated procedure. For abdominal operations which will probably require less than one-and-a-half

hours of anæsthesia the single-dose technique is indicated. Nupercaine or amethocaine is the agent of choice. My impression is that with high spinal analgesia the anæsthetist can obtain more control with heavy nupercaine than with the light solution.

For operations which will be protracted, say from two to four hours, a *continuous or fractional anæsthesia* has many advantages and has been employed with success for a number of complicated gastric and pancreatic operations and for the meticulous painstaking dissections which are called for in reparative operations upon the common bile duct. By using the safest of all local agents—procaine (100 mg. according to height and weight, followed by 50 mg. at half-hourly intervals)—a carefully controlled high spinal analgesia may be produced and supplemented by fractional dosage.

I prefer the *Lemmon technique* with its special mattress and the use of the small-bore malleable needle to the *Tuohy method* for which a *large-bore* needle and a No. 4 ureteral catheter are required. The catheter has to be skilfully adjusted, otherwise it may become dislodged or even withdrawn when the large-bore needle is removed. 5% of the reported cases in Tuohy's series suffered from severe headaches. In our series of 40 gastrectomy cases the incidence was approximately 10%. These headaches were probably caused by the large needle hole which remained in the theca for some days. I decry the use of spinal block in infancy and in old age, in feeble subjects and in patients suffering from the effects of shock, low blood pressure, or hypertension associated with arteriosclerosis. My affection for spinals, and particularly those of the continuous type, has waned and chilled appreciably since the advent of curare.

(*e*) *Intercostal block:* Intercostal block, either posterior or mid-axillary, may be combined with splanchnic block if no covering general anæsthetic is used. By paralysing the lower six intercostal nerves the effect is like that produced by the curarizing drugs. Unlike curare, however, there is no antidote, and if the operation is shorter than expected the patient is faced with three hours of partial respiratory paralysis. Cases of serious damage to the pleura and lung have been reported. The technique of infiltrating the lower six intercostal nerves is slow, tedious and exacting—muscular relaxation is whimsical or impish even when the amethocaine or nupercaine solution is bolstered with cyclopropane or by splanchnic block.

(*f*) *Abdominal field block combined with anterior splanchnic block:* I have used this method, which was popularized by Finsterer, in over 100 gastric operations with a mortality of about 3%. A large quantity of procaine 0·5% solution (without adrenaline) is employed using as much as 100 c.c. for the Braun block. As a rule, no pre-anæsthetic, intravenous barbiturate or light covering general anæsthesia is given, as it is desirable to reduce the toxic load to a minimum. This procedure is specially recommended for operations upon the stomach, duodenum, gall-bladder and pancreas, in wasted, feeble or aged patients, and also for those suffering from certain concomitant cardiac, pulmonary, renal or hepatic disorders. As the surgeon himself gives the anæsthetic and as the method is generally unpopular among anæsthetists, it is advisable to put these cases at the bottom of the operation list. It is advisable to strap the patient to the table as there is a strong tendency for him to move his body or limbs during the induction and when traction is made upon the stomach or mesentery. It is also desirable to have a junior anæsthetist sitting in the corner of the operating room—just in case of emergency!

Curare

Curare is the answer to the surgeon's prayer. I use the word curare to include all the curarizing drugs in clinical use, such as Tubarine, Flaxedil, &c. (*see* Table I).

Curare produces profound muscular relaxation—a flaccid paralysis—with certainty and rapidity by efficiently blocking the impulses of the myoneural junction. As it has no anæsthetic or hypnotic properties, it has to be supplemented by pentothal, gas and oxygen, cyclopropane, or minimal ether. A good sequence is cyclopropane-curare with an endotracheal tube in place. It is best to intubate before the operation is started, as the anæsthetist can then easily manage the respiratory depression which so frequently occurs after the curare has been injected. For abdominal operations curare should not be given to patients who are not anæsthetized, and it is imperative for the anæsthetist to be positive that they are always *under* anæsthesia during its use. The sensation of impending disaster which follows paralysis of the muscle of swallowing and of the limbs may be a terrifying and haunting experience for a patient.

For the abdominal surgeon curare has few contra-indications; for the anæsthetist there are perhaps more. It is being used throughout this country with increasing frequency and confidence. The combination of light anæsthesia and profound muscular relaxation makes

a special appeal to the abdominal surgeon. I will not stress one of its main dangers, namely that of returning the patient to the ward with intercostal paralysis.

To those surgeons who rejoice in closing a flaccid abdominal wall but who fear the respiratory depression which follows in the wake of curare, I would presume to offer these words of advice: sew the peritoneum and posterior sheath of the rectus muscle quickly but with security, but approximate the remaining layers of the wound accurately and safely with a studied lethargy. It is always comforting to the surgeon to hear his patient breathing deeply and evenly when he is wheeled away from the operating room.

TABLE I.—CURARIZING DRUGS IN CLINICAL USE

Proprietary name	Chemical name	Site of action	Antagonist
Intocostrin ..	Extract of curare; mainly *d*-tubocurarine chloride	Myoneural junction block	Neostigmin Physostigmin
Tubarine ..	1% solution of *d*-tubocurarine chloride	Myoneural junction block	Neostigmin Physostigmin
Myostatin ..	1% solution of *d*-tubocurarine chloride	Myoneural junction block	Neostigmin Physostigmin
Myanesin ..	oc: B-dihydroxy-x-(2-methyl-phenoxy)-propane	Depressant action on parts of nervous system between cortex and spinal cord, may also depress function in basal ganglia, brain-stem and thalamus. Does not produce myoneural block in clinical doses. In smaller doses depresses reflex excitability of spinal cord	Picrotoxin
Lissephen (in U.S.A.)	"		
Flaxedil	Tri-(diethylaminoeth-oxy)-benzene	Myoneural block	Neostigmin Physostigmin
Syncurine ..	Decamethonium iodide (C.10, Bistrimethyl-ammonium decane diiodide)	Myoneural block	Pentamethonium iodide (C.5, Bistrimethyl-ammonium pentane diiodide)
Eulissin	Decamethonium iodide (C.10, Bistrimethyl-ammonium decane diiodide)	Myoneural block	Pentamethonium iodide (C.5, Bistrimethyl-ammonium pentane diiodide)
—	Dihydro-B-erythroidine	Myoneural block	Neostigmin Physostigmin

CONCLUSIONS

(1) Satisfactory muscular relaxation can be achieved by a variety of reliable agents and methods. These in turn are dependent upon a number of factors which have been briefly discussed. No hard and fast rules can be laid down, as each patient is a special problem.

(2) The sequence pentothal-gas-oxygen-ether is safe, popular, and adequate for most straightforward abdominal operations. Muscular relaxation is good but modest.

(3) Curare combined with a covering anæsthetic is rapidly gaining in popularity, and is especially indicated in fit, strong, muscular subjects, and also for the majority of prolonged and complicated intra-abdominal procedures.

(4) High spinal analgesia employing the single-dose technique has many adherents, but the continuous or fractional method of Lemmon or Tuohy, owing to a number of unpleasant post-operative sequelæ which are prone to occur, is open to many criticisms and is unlikely to gain favour in this country.

(5) Field block combined with splanchnic anæsthesia, if suited to the surgeon's temperament, is an excellent method in selected cases.

(6) A plea has been made for the establishment in all large hospitals of a *post-anæsthesia room* and also for regular *out-patient sessions for anæsthetists*.

(7) The debt of modern surgery to anæsthetists is indeed great; many of the striking advances in surgery, and especially in abdominal surgery, could not have been accomplished without their work, skill and courage.

Dr. M. D. Nosworthy: There seem to me to be some points—apart from details of anæsthetic agents—which are of sufficient importance to justify their re-emphasis.

Unless it is prevented by drugs from so doing, a muscle will contract when stretched by the surgeon. The more forceful the movements of the operator, the more completely must the muscles be put out of action—if relaxation is to be maintained. We anæsthetists prefer—and so would patients if they knew anything about it—the gentle surgeon because we will require to use smaller doses of drugs. It is up to us, however, to provide a sufficient degree of muscular relaxation to cover the individual surgeon's needs because the retraction of unrelaxed muscles is bound to increase the patient's post-operative discomfort. Another reason why we prefer the gentle surgeon is that—besides increasing post-operative morbidity—the rougher the manipulations inside the abdomen—particularly when these are unexpected—the more flaccid must the muscles be kept to prevent their natural protective spasm in response to such insults.

It seems definite to me that, when muscular relaxation is fully secured *before* the patient is irritated or stimulated at all, the dose of general anæsthetic and/or curare required to produce this state is reduced, and not only does this relaxation last longer but it can be easily reproduced at any time. Anticipating the surgeon's requirements is always worth while. It is also worth while testing every patient's muscular strength and assessing his reflex irritability *before* operation since some patients have little muscular power and next to no reflex irritability. In such individuals perfect anæsthesia is easily produced without the need for deep anæsthesia or for curarization.

Muscular relaxation must not be confused with surgical access. There is a limit to which a small incision will open whatever the degree of muscular paralysis. It is not uncommon for a surgeon, during appendicectomy, to pull out the cæcum through a small grid-iron incision, and the difficulty which he experiences in returning it is more often due to partial strangulation of the cæcum than to lack of muscular relaxation. A paramedian incision, an inch or two greater in length, may well increase the patient's post-operative comfort; and it would be helpful if some surgeons would remember that the costal margin is a rigid structure which is beyond the capabilities of even the most modern anæsthetist to relax.

I trust that use of the gall-bladder "rest" is a thing of the past; and it is worth bearing in mind—when dealing with handicapped patients—that a Kocher's incision requires a lower concentration of drugs than does a paramedian. The same applies to a transverse incision for a procedure such as transplanting the ureters.

Gas in the stomach may be responsible for difficulty in closing a hole in the diaphragm which the surgeon attributes to inadequate muscular relaxation. Easy closure may follow the passage of a stomach-tube. I do not know whether surgeons have yet tumbled to the fact that the gas which they find in the stomach at operation these days has often been pushed there by the anæsthetist prior to intubation after thiopentone and curare.

Respiratory obstruction, anoxia and excess CO_2, are well known as factors militating against muscular relaxation. This is no time to go into the pros and cons of endotracheal anæsthesia for abdominal operations, but it is worth emphasizing that early intubation—with insufficient drugs on board—is a frequent cause of lower respiratory obstruction; and I wonder how often this state occurs as a result of the facility with which early laryngoscopy can be performed with Professor Macintosh's instrument. I am not saying anything against this laryngoscope, but only against the way it is sometimes used.

Hyperventilation favours muscular relaxation. If a patient is initially rendered apnœic and completely relaxed with a single injection of thiopentone and curare, and subsequently ventilated with, say, a 75/25 nitrous oxide-oxygen mixture, he will often remain relaxed throughout an abdominal operation. Although the curarizing effect has long since worn off, the abdominal muscles will remain completely flaccid so long as the patient is kept apnœic. As soon as his carbon dioxide is allowed to reaccumulate, however, every trace of abdominal relaxation disappears at the first active expiration the patient makes. Of course, if hyperventilation is attempted before the patient is adequately anæsthetized or curarized, activity of the Hering-Breuer reflex is likely to result in expiratory muscular spasm.

Turning to the drugs and techniques which are commonly used to produce muscular relaxation, if progress is to be made the advantages of any method—new or old—must be carefully weighed against the hazards associated with its use, and the conditions provided in the operating theatre must not be divorced from those found during the post-operative period. This is not only a plea for personal record-keeping, but also a suggestion that watching another anæsthetist's performance is only complete when the post-operative behaviour of his patients has been studied in the wards.

Spinal analgesia, as we all know, produces perfect muscular relaxation; but—to mention one point only—is the risk of paralytic ileus, following an abdominal operation, greater after spinal than after other methods of anæsthesia? This complication has occurred with sufficient frequency in my practice to make me wonder whether there is sympathetic over-activity when it once more comes into action?

I personally dislike having patients awake during operations, and, therefore, have nothing to say about pure regional methods.

There is no doubt that ether can produce perfect muscular relaxation and, being slow in action, it can teach the young anæsthetist a great deal about anæsthesia. The trouble starts when he tries to hurry up anæsthesia, and I think that the possibility of injecting a small dose of curare—if a smooth induction is taking too long—may still make nitrous oxide-oxygen-ether the safest method of anæsthesia for abdominal operations by the young resident anæsthetist.

In order to reduce the necessary concentration of inhalation agent, I was—for several years—in the habit of using, in addition, an intercostal nerve-block with nupercaine for laparotomies. The operative condition of these patients seemed fairly satisfactory to me, and so did their post-operative progress.

With cyclopropane I soon found that *my* robust patients—besides often having cardiac arrhythmiæ during operation—too frequently went through a nasty phase of circulatory depression in the early post-operative period. I therefore reverted to my combined method.

For the poorer-risk patients, however, I was satisfied with cyclopropane, and I have the record of one patient whose blood pressure and pulse at the end were the same as the pre-operative readings although the peritoneum had been wide open for five and a half hours. For all that I would not recommend pure cyclopropane to the young anæsthetist for securing muscular relaxation, since it is a drug which requires knowing well and I see little point nowadays in using it alone for this purpose.

In recent years I too have turned my attention to the derivatives of curare, and there are several points which I should like to bring up for discussion in connexion with the use of these drugs.

There can be no doubt that an injection or two of curare is easier and quicker to do than a regional block. When muscular relaxation is obtained by blocking the necessary intercostal nerves, spontaneous respiration is adequate to fulfil the patient's metabolic needs. When curare has been used this is not always the case; and even to-day unfortunately one too often sees a patient hitched to a Boyle's machine and getting along inefficiently by himself as best he can. When shallow breathing calls for assistance, synchronization with the patient's own efforts is not always easy; full control is more satisfactory. The vast majority of patients come to no harm when artificial ventilation is properly carried out—the inspiratory build-up of pressure should be gradual and the expiratory release prompt.

It is quite entertaining to take blood-pressure and pulse readings at half-minute intervals after an injection of thiopentone and curare—given for the purpose of intubation before laparotomy. Most patients' cardiovascular systems are fortunately resilient, but I think that the possible consequences of artificial ventilation—as set down in Dr. Dripps' paper (1949)—are worth bearing in mind when a handicapped patient has to have an abdominal operation. Another point—an experienced ward-sister at one hospital where this technique is in common use remarked "Patients aren't sick nowadays but so many of them have sore throats after operation. Why should this be so?"

When thiopentone-curare-nitrous oxide-oxygen is used to maintain adequate abdominal relaxation efficient spontaneous respiration often seems to be absent for a considerable time and hiccough appears to be a frequent operative complication; whereas when cyclopropane—or ether for that matter—is substituted for the nitrous oxide-oxygen and the inhalational contribution is rather greater, the breathing seems to be spontaneous and efficient sooner and hiccough does not occur.

Now, if a curare derivative is to be used to ensure relaxation for closing the abdomen, is one drug preferable to another? Some recent work on Flaxedil seems to show that, after a similar degree of curarization the respiratory amplitude is returned to *normal levels* by an injection of prostigmine and atropine much sooner in the patient who has received this drug. This brings us to the post-operative state of the curarized patient. It is obviously wrong to return to the ward a patient who is not breathing properly—the risk of respiratory fatigue later on is great. Is there any harm in giving antidotes and analeptics? Is it possible for the effect of the antidote to be too short-lived, and for the patient who has received an excessive dose of relaxant to become re-curarized?

For what it is worth, I personally am against the use of antidotes. For me they would take away all the fun—I hesitate to say the art—of anæsthesia. I myself give an ample initial dose of curare, either to begin with or during a thiopentone-cyclopropane induction, and, if necessary, I give subsequent injections but *never towards the end of an operation.* By anticipating the closure and, if necessary, increasing the concentration of cyclopropane, and sometimes by hyperventilating the patient, I expect to have him self-supporting by the finish.

For abdominal operations I personally use curare so that I can slowly build up an adequate concentration of cyclopropane or cyclopropane-ether without ever having to force the inhalation agent, in much the same way as I use thiopentone with nitrous oxide-oxygen or cyclopropane, for superficial operations. I am glad to observe a tendency to replace later injections of thiopentone by intravenous injections of morphine or pethidine—thereby reducing post-operative pain and the risk of restlessness and the complications which may ensue.

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Anoxia and Anæsthesia

By B. G. B. LUCAS, D.A.

IN 1875 Claude Bernard in a monograph on the relationship between anæsthetic agents and asphyxia concluded that their analgesic effect was due to interference with the oxidation of the nerve cells of the brain. This conclusion was ignored and no interest was taken in the relationship of anoxia to medicine until the early twentieth century. In 1919 Haldane stated that anoxæmia not only stops the machine but wrecks the machinery. This is undoubtedly true, but it is not sufficiently appreciated that the anoxia can be of any type, anoxic, anæmic, stagnant or histotoxic, or a combination of any of these. It is the state of tissue oxygen lack in the brain which is related to anæsthesia. How a cell may fail to receive an adequate oxygen supply is outside the scope of this paper, but the end-result is a depression of cell metabolism. This gives an adequate definition and explanation of general anæsthesia.

There have been many theories of anæsthetic action. About one hundred years ago von Bibra and Harless (1847) established a correlation between anæsthetic action and the relative solubilities of certain substances in the lipoid and non-lipoid constituents of the cell. This theme was elaborated by Meyer (1901) and Overton (1901) independently, who both showed that there was a connexion between anæsthetic activity and the distribution coefficient of certain drugs in a lipoid water system. Lillie (1916) demonstrated that anæsthetic action was related to viscosity and surface tension, and later Gellhorn and Weidling (1925) described an alteration in the permeability of the plasma membrane of the cell under anæsthesia. These theories indicate how the anæsthetic drug may gain access to the cells, but they do not afford any explanation of the drug's action. The functions of the cerebral cortex are readily depressed by altering its blood supply and there is much evidence of the relationship between the physiological activity of the brain and its utilization of oxygen and glucose. In 1932 Quastel and Wheatley showed that anæsthetic agents decreased the oxygen uptake of brain tissue. In a variety of animals, they found that the respiration of the brain was inhibited by drugs, such as ether, chloroform and the barbiturates, in concentrations which caused deep narcosis. Furthermore, they found that this effect was rapid and reversible and that the sensitivity of the brain was in marked contrast to that of other organs. They demonstrated that the oxidation by the brain of glucose, sodium lactate and sodium pyruvate was inhibited more readily than was that of glutamic acid, whereas the oxidation of sodium succinate was unaffected (Quastel, 1943). This implies that anæsthetic drugs exert their inhibitory effects at two possible stages, either by interfering with the transfer of hydrogen from reduced cozymase to flavoprotein, or by preventing the oxidation of flavoprotein by the cytochrome system. Grieg's experiments (1946, 1947) suggest that the inhibition probably occurs at this latter stage. In guinea-pigs deprived of vitamin C, the action of nembutal is prolonged and this effect is considerably reduced when the animals are given ascorbic acid; also its addition to brain suspensions

in the presence of nembutal diminishes the inhibition of glucose metabolism. She postulated that the function of ascorbic acid is to offer an alternative route for the oxidation of carbohydrate, by providing a by-pass between the flavoprotein stage and cytochrome-c. From this and other evidence, it is concluded that anæsthetic agents exert their action by interfering with glucose oxidation, causing a depression of brain respiration; in short, a state of histotoxic anoxia.

It is well known that the cells of the central nervous system are susceptible to anoxia. If it is so severe as to cause immediate death, then no histological change is demonstrable; with prolonged anoxia ante-mortem changes become evident and are most pronounced in the cells of the cerebral cortex, the Purkinje cells of the cerebellum and in the basal ganglia and hippocampus. Dixon and Meyer (1936) have shown that these areas have the highest oxygen uptake in the brain, and other workers (Spielmeyer, 1930; Scharrer, 1940; Campbell and Forster, 1944; Nilges, 1944) have independently demonstrated that they have the poorest blood supply.

The histopathological changes of anoxic anoxia have been described by Yant and his colleagues (1934) who demonstrated in dogs and rats two types of abnormal nerve cell, some shrunken and staining diffusely, others showing various degrees of chromatolysis. Most damage was found in the granular layer of the cerebral cortex and the thalamus. They also noted that the changes from carbon monoxide poisoning were identical. This latter work was confirmed by Lewey and Drabkin (1944). Buchner and Luft (1935) describe damage in the brains of guinea-pigs kept at low oxygen tension; changes included marked nuclear degeneration, vacuolation of the cytoplasm and loss of Nissl substance in the ganglion cells in the floor of the fourth ventricle. Similar but less marked abnormalities were observed in the Purkinje cells of the cerebellum. A review by Lewis and Haymaker (1948) of 75 deaths due to anoxia in aircrew during the second world war revealed changes similar to those in animals.

Ischæmic anoxic changes, both stagnant and anæmic, were described in 1925 by Spielmeyer. He found four main types: cell swelling, in which the cell stains poorly and the chromidial substance is disintegrated; shrinkage, in which the chromidial substance stains darkly and may be in clumps; cell liquefaction or homogenization, where it is pale with a small metachromatic nucleus; and coagulation, in which the cell is pale, shrunken and, sometimes, disintegrating. Similar changes were noted in the brains of cats after acute anæmia by Gildea and Cobb (1930). Dublin and Brown (1942) provide clinical confirmation, citing one case of delayed death following asphyxia from hanging.

There are three types of nerve cell change associated with acute anoxia. The first is an œdematous one and corresponds to Spielmeyer's cell swelling. The cell stains palely and shows occasional vacuoles in the cytoplasm, and the Nissl substance is characteristically fragmented into fine dust-like particles. In the second type, the shrinkage stage, the whole cell is shrunken with a darkly staining nucleus, its outline becomes angular and the Nissl substance is easily definable and aggregated together. The third type represents the stage of disintegration; in its worst form, the cell is hardly discernible and is surrounded by small round neuroglial cells, the so-called satellitosis. At an earlier stage, the cell is pale and homogeneous in character.

In death from anoxia all types of cell disturbance can be found and from a preponderance of any one, the amount and time of anoxia can be deduced. Weinberger, Gibbon and Gibbon (1940) demonstrated changes in the cerebral cortex of the cat by complete arrest of the circulation for varying periods of time and found that three minutes produced cell swelling, whereas seven and a half caused disintegration.

It may be argued, with reason, that the effect of hypoglycæmia is primarily anoxic, since the oxygen which is freely available has no substrate to metabolize. The literature on the subject of cerebral damage in hypoglycæmia has been reviewed in great detail by a number of authors (Weil, Liebert and Heilbrunn, 1938; Baker, 1939; Lawrence, Meyer and Nevin, 1942). All of them agree that the changes are identical with those of anoxic or ischæmic anoxia. Lawrence, Meyer and Nevin (1942) emphasize the resemblance to anoxic poisoning, such as carbon monoxide and cyanide, as well as ether.

The changes due to anoxia are the same as those found following over-dosage with anæsthetic agents. Steegmann (1939) called attention to the similarity of the lesions after avertin and cyclopropane and those due to ischæmic anoxia. Similar changes with cyclopropane anæsthesia were reported by Gebauer and Coleman (1938). Lenahan (1943) described shrinking, distortion and pyknosis in the nerve cells of the cerebral cortex following death under ether anæsthesia. The effect of the barbiturates on the brain has been studied by a great number of authors. Hartman (1937) poisoned dogs with amytal and showed that the main change was marked vacuolation and degeneration, with clumping of the Nissl sub-

stance. This had been reported previously in experimental medinal poisoning by Nakamura (1933). Hassin (1939) described three human cases of luminal poisoning, where the main cell changes consisted of swelling, chromatolysis and occasional disintegration. Recently, Jervis and Joyce (1948) have recorded one death following overdosage with a barbiturate and an opiate. Here, the changes were similar to those already described.

Whether nitrous oxide achieves its effect by a purely asphyxial action, that is a reduction in the blood oxygen tension, or whether it has a direct anæsthetic action is controversial. There is no doubt, however, that the brain changes after death from nitrous oxide are anoxic in character. Lowenberg, Waggoner and Zbinden (1936) describe one man who did not recover consciousness after the administration of nitrous oxide and died sixty hours later. Post mortem there were scattered petechial hæmorrhages throughout the brain and the third, fifth and sixth cortical laminæ were destroyed, showing many degenerating neurons. In the mid-brain there was also marked damage. Some nerve cells were shrunken with pyknotic nuclei, others appeared irregular or elongated in shape, with pale, slightly granular cytoplasm and deeply staining nuclei. These authors point out that this damage cannot be caused by respiratory failure and resuscitation, and, in a later paper (Lowenberg and Zbinden, 1938), they quote several more cases that showed advanced degeneration of nerve cells despite the absence of respiratory failure.

Courville (1939), in his monograph on the *Untoward Effects of Nitrous Oxide Anæsthesia*, also describes the nerve-cell damage characteristic of anoxia. He stresses the delayed effect, although in a previous paper (1938) he records several cases that died within a few hours of nitrous oxide anæsthesia in which cell changes were observed.

It can be assumed, therefore, that anæsthetic agents achieve their effect by a histotoxic anoxic action and that the change in the central nervous system following overdosage is the same as that with any other type of anoxia. The literature has been extensively reviewed by Hoff, Grenell and Fulton (1945) who reach the same conclusion. If this be so, then some of the effects observed with ordinary anoxia might be expected with anæsthetic agents.

A survey of the literature discloses an apparent discrepancy between the severity of damage and the amount of anoxia. A clue is found in the work of Thorner and Lewy (1940) who showed that there was a progressive and accelerated cerebral change with repeated doses of anoxia. Guinea-pigs were submitted to severe asphyxia daily, by placing them in a chamber filled with nitrogen, until respiration ceased, and then were removed and resuscitated. After nine to twelve such exposures, the animals were killed and examined. The brains showed a progressive destruction of nerve cells in proportion to the number of exposures.

Prior to this work Dellaporta (1939) described experiments in which he subjected guinea-pigs to low oxygen tensions by decompression in air to approximately one-third of an atmosphere (250 mm. Hg) for periods up to one hundred hours. If the animals were killed immediately, no changes in the central nervous system were demonstrable, but if they died some hours after their exposure to low pressure, then lesions appeared. Merk (1940) subjected guinea-pigs to low atmospheric pressure (198 mm. Hg) for one hour every day until the animals succumbed; he found nerve-cell changes in the brains of all of them.

All this experimental evidence suggests that repeated or long periods of anoxic anoxia have a cumulative action on the brain. In the light of this, certain other investigations become relevant. Mott, Woodhouse and Pickworth (1926) found that large and repeated doses of various barbiturates produced chromatolysis and some nuclear and cytoplasmic changes in the Purkinje cells of the cerebellum, as well as in the cells of the medulla and cerebral cortex. The greatest change occurred when the doses were repeated over a long time. Again, in dogs who had been given a daily dose of a barbiturate for three and a half years, Seevers and Tatum (1931) observed marked shrinkage and homogenization of cells throughout the cerebral cortex, basal ganglia and thalamus. Heilbrunn, Liebert and Szanto (1945) reported one case of a man given to inhaling chloroform daily for twelve years and who finally died of diphtheria. His brain showed a great reduction of the Purkinje cells in the cerebellum and marked reduction and shrinkage of the nerve cells of the basal ganglia. These workers describe the pyknotic, shrunken stage of anoxia which is associated with chronic prolonged exposure. Again, Hurst (1944), reviewing the results of experimental cyanide and sodium azide poisoning, showed that most changes are found when repeated doses are given over a long period.

To discover whether this conception of accumulation of anoxic effects is true, a series of experiments were carried out in 1946 (Lucas, 1946). Rats were kept in a gas-tight chamber, to which low oxygen nitrogen mixtures could be admitted, for a period ranging from a few hours to many days. Initially, continuous exposures of oxygen tension of 3 to 4% were used and the animals survived for a period of approximately half to one hour.

As the oxygen content was raised, so the survival time lengthened until with 9% oxygen it was approximately three days. In other experiments the animals were subjected to the same degree of anoxia (9% oxygen) for periods of seven hours daily, when their survival time was approximately nine to ten days. This compares directly in time (63 to 70 hours) with the rats of the previous group which were anoxic continuously for three days (72 hours). Microscopic examination of the brain in the acute experiments revealed very little, but as the anoxia became more prolonged, evidence of damage appeared.

Further experiments were conducted to find out whether these changes could be produced with anæsthetic agents. In one series 0·5% chloroform vapour in oxygen was used and in another 10% oxygen in nitrous oxide. Again, severe damage could be detected after approximately the same length of time, whether it was two or three days of continuous exposure, or a week or more intermittent.

A histological study of this material showed that although the anoxic effects were cumulative, there was a stage below which recovery was possible. It was noted that some animals which had been allowed to recover and had not died during the experiment, showed less damage than those which succumbed. Under conditions of more prolonged anoxia, the animals which were removed from the chamber and killed some days later showed more change. It was found that in the former group the damage was of the acute swelling type; the latter produced pyknotic, or destroyed cells.

From this experimental work there seems little doubt that the effect of anoxia can be cumulative, although some reversibility of action is possible. This hypothesis was originally propounded by Buzzard and Greenfield in 1923.

The biochemical change taking place inside the cells under anoxic conditions must be studied in order to explain this reversibility. From the histology, the first effect is an intracellular œdema; later it may be extracellular as well. It is possible that this œdema is the reason for some of the discrepancies observed by various authors. Œdematous tissue is difficult to study histologically because of the variable action of fixatives.

The action of all fixatives is essentially the same, that is to withdraw water from the tissue and substitute a precipitating agent for the protein. Perhaps the disrupted anoxic nerve cell is not an absolute entity in itself, but rather more the effect of too rapid fixation. Certainly pseudo-anoxic changes can be obtained in normal brain by bad fixation, or as a result of post-mortem autolysis. Again, this œdema may, by itself, cause further interference with cell metabolism, so that after the anoxic insult has ceased, its effect may continue and, if a further dose of anoxia occurs before this œdema has subsided, then more damage will occur and become irreversible. A study of the literature shows that this cumulative effect does not necessarily have to be with the same type of anoxia, any combination being equally harmful.

This has great importance in clinical anæsthesia. Long periods of anæsthesia may cause œdema in the cell, which will disappear as long as further anoxic insults are not superadded. Shock, hæmorrhage or defective ventilation post-operatively may, in themselves, produce enough anoxia to render the change in the cell irreversible. This may occur because the body's normal compensatory mechanism for anoxia, for example an increase in cardiac output and respiratory tidal volume, does not always occur in the deeply anæsthetized subject. Again, repeated periods of anæsthesia may be harmful unless the interval is long enough for the cell to recover completely.

Permanent changes resulting from anoxia during anæsthesia producing mental damage have been discussed fully by Batten and Courville (1940). Many cases have been described, varying from complete dementia to a mild personality change. One more can be added to the latter group.

This was a man of 54 years who was being operated on for a right inguinal hernia under epidural anæsthesia with the addition of evipan, nitrous oxide and oxygen. Shortly after the nitrous oxide and oxygen had been started the patient became very cyanosed and remained so throughout the operation. Towards the end, respiration failed completely and had to be maintained artificially. It was then observed that the nitrous oxide by-pass on the anæsthetic machine had been turned on in error, so that the patient had been receiving approximately 5% oxygen instead of 25%; this fault was rectified and the patient's colour improved. Natural respiration returned after thirty minutes, by which time the operation had been concluded. The patient took six hours to recover consciousness but when he did, he was maniacal and had to be restrained for a further period of twenty-four hours. After this, he appeared to be fairly normal, but one week later his relatives volunteered the statement that he was quite a different person; having previously been morose and argumentative, he was now placid and pleasant. This was borne out by the evidence of two nursing sisters, one of whom was the medical ward sister where he had been resting for three weeks prior to operation. She stated that what the relatives had said about him was quite true and that he had

been a very difficult patient; the surgical ward sister, on the other hand, said that she had never had a more co-operative patient.

This in itself is not conclusive, but it does suggest that anoxia can, under suitable circumstances, have a beneficial effect. In the field of psychiatry, daily periods of acute anoxia have been used with good effect in the treatment of schizophrenia (Himwich, Alexander and Lipetz, 1938). Possibly the mechanism in these cases is the production of further permanent mental damage, so making the subject more acceptable to society.

The mildest anoxic change that may occur in brain cells following anæsthesia can cause post-operative complications. Restlessness and delirium, which are sometimes seen, are often anoxic in origin. Frequently these occur following anæsthesia which has not proceeded smoothly; in those cases where difficulty with ventilation has been experienced, for example in thoracic surgery where an excess of secretion has prevented the anæsthetist from maintaining adequate oxygenation of the patient throughout the operation. Another common group is tonsillectomy in the young adult where there has been some respiratory depression and obstruction. In these cases recovery is often delayed and there may be mental confusion; they are stated to be restless or hysterical. This syndrome is commonest in the age-groups 14 to 25 and over 60. In the former ultimate recovery is probable, but in the over sixties, the reverse is true and psychotic changes may occur. These are frequently regarded as being due to premature senility, or else to cerebral metastases if the patient is suffering from malignant disease. In this condition heavy sedation for the restlessness is dangerous because it may produce further anoxia in the cell, so that irreversible damage may result. Restlessness and delirium with recovery have been reported as complications of the anoxia that occurs at high altitudes (Church and Loeser, 1938).

Experimentally it has been shown that the œdematous cell can rapidly become irreversibly damaged; therefore, when this œdema occurs it should be removed as quickly as possible. For example, following the severe anoxia of cardiac arrest, the heart may be re-started but the patient will be deeply unconscious. As soon as the heart resumes its beat, treatment for the œdema should commence. The withdrawal of fluid from the brain by hygroscopic or osmotic methods is the basic principle in the removal of cerebral œdema. The best is the intravenous use of concentrated human serum in a dose not exceeding 50 ml. per hour. Too rapid dehydration may produce convulsions.

In the treatment of cardiac arrest under anæsthesia, it is essential to obtain an adequately oxygenated cerebral circulation; time is vital. Kabat, Denis and Baker (1941) found that eight minutes of cerebral anæmia produced irreversible changes in the dog. These animals were not anæsthetized, hence had no histotoxic anoxia. In man under anæsthesia, the time is reduced to three minutes. To obtain adequately oxygenated blood, artificial respiration must be started at once. Simultaneously, the heart must be made to function as a pump by means of cardiac massage. Intracardiac injections with adrenaline or any other drug are useless because it is unlikely that the heart will resume beating effectively, but will merely fibrillate and consume further valuable oxygen and time (Dripps, Kirby, Johnson and Erb, 1948). The correct procedure is manual cardiac massage and artificial respiration until such time as the circulation to the head is seen to improve; then intracardiac adrenaline can be used. This routine was suggested by Hamilton Bailey (1941). That cardiac massage is effective in maintaining an adequate cerebral circulation has been demonstrated by Johnson and Kirby (1949) who obtained a blood flow of 50% of normal in the dog by manual compression of the heart through the chest. Simultaneous occlusion of the abdominal aorta further increased the cerebral flow.

The rapidity with which the heart beat returns to normal is dependent upon the reason for which it stops. If this has been caused by stimulation of the vagus, either directly or indirectly, then, with cardiac massage, the heart will soon start again. Commonly there are no premonitory symptoms of impending death, the so-called "status lymphaticus". Secondly, the heart may stop because of prolonged anoxia, which may result from asphyxia, excessive doses of anæsthetic agents, shock or hæmorrhage. Here, there may be a delay in the return of an effective beat. Thirdly, where there have been signs of pre-operative myocardial disease or where there has been excessive anoxia, the heart will be irreversibly damaged and will never function again. Under these conditions, it will be toneless on palpation.

The following is a record of one case of successful cardiac massage with complete recovery.

A woman of 53 years was operated upon for toxic adenoma of the thyroid under rectal pentothal, nitrous oxide and oxygen anæsthesia. The dose of rectal pentothal (3 grammes) was excessive, but the thyroidectomy was completed without incident. She did not recover consciousness for several hours. Her post-operative recovery was uneventful except for attacks of paroxysmal tachycardia which were controlled by quinidine. Three weeks later, a stitch abscess developed which necessitated incision. She was given pentothal 0·4 gramme intravenously and almost at once her heart and

respiration stopped simultaneously. Artificial respiration was immediately commenced and cardiac massage performed. The interval between the cessation of the heart and effective massage was within three minutes. Her heart did not commence to beat effectively for a further five minutes, but when it did so, its beat was strong, at a rate of ninety per minute. Natural respiration re-established itself ten minutes later. From the onset of cardiac massage her colour was good. After one hour, she was deeply unconscious with no reflexes and moderately dilated pupils, but her respiration was regular and not stertorous. Six hours later, her limbs were spastic but her pupils showed a light reflex. After twenty-four hours she was still unconscious, but responded to painful stimuli. 50% intravenous glucose therapy was commenced. After a further twelve hours, she recovered consciousness with no abnormal neurological reflexes, but she was demented. One week later, she was completely child-like, her memory being that of her own childhood and when asked to write her name, she wrote her maiden name in a childish scrawl. Slowly her condition and memory improved and three months after her cardiac arrest she left hospital apparently normal apart from some loss of memory of recent events and a slightly childish personality. Six months later, she had completely recovered and neither her relatives nor her medical attendants could find anything wrong with her.

In anoxic conditions, the type must be identified before treatment is commenced. If it is histotoxic, which includes most anæsthetic agents, then the anoxia occurs in the tissue cells because of inhibition of part of the tissue oxygen enzyme system. In barbiturate poisoning, it is the oxidation of glucose which is disturbed; if a different substrate could be substituted, then tissue metabolism could continue. The oxidation of succinic and glutamic acids remains unaffected by the barbiturates and sodium succinate has been used successfully in the treatment of barbiturate poisoning (Soskin and Taubenhaus, 1943). Glutamic acid has been used effectively in the treatment of insulin coma and in depressive psychotic states where there was evidence of defective oxygen utilization (Mayer-Gross and Walker, 1947).

In other forms of anoxia, the oxygen supply to the tissues must be improved. In the anoxic variety, the oxygen content in the lungs should be increased; in shock and hæmorrhage anti-shock measures, including blood transfusions to raise the oxygen-carrying properties of the blood, must be instituted. If, in spite of these methods, the oxygen reaching the tissues is still at a low tension, an attempt should be made to "boost-up" tissue oxidation so that metabolism in the cell can continue under these conditions. In 1941 Stewart, Learmonth and Pollock investigated the use of ascorbic acid in the treatment of experimental shock in cats and reported favourably on it. Experimentally, both ascorbic acid and methylene-blue increase the tolerance of adult rats to anoxia (Lucas and Peterson, 1941). On theoretical grounds, the tissue oxygen enzyme cytochrome-c, which has recently been synthesized, should be of value and the effect of this substance is at present being investigated.

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Section of Pædiatrics

President—W. W. PAYNE, M.B., M.R.C.P.

[*January* 27, 1950]

Two Cases of Duplication of the Alimentary Canal.—J. R. D. WEBB, O.B.E., M.R.C.P., D.P.H., D.C.H.

Professor William Ladd, of Harvard and Boston, has suggested that the term Duplication of the Alimentary Tract might be used instead of Mesenteric Cyst, Enterogenous Cyst, Diverticulum, &c. He says that the ileum is the most frequent site for such duplication, although it may occur anywhere in the alimentary tract from the œsophagus to the rectum.

These cysts cause symptoms either by producing bleeding into the parent loop or by causing intestinal obstruction by pressure. Sometimes owing to ectopic gastric mucosa, they may cause ulceration and even perforation.

The constant feature is that the duplications of the parent loop share the same muscular coat and therefore they cannot be removed without damaging the parent loop; furthermore the blood supply to the normal bowel has to cross the duplication.

CASE I.—K. W., male, aged 7 years.

Home conditions poor.

Past history.—Apparently normal child.

Present history.—Abdominal pain with vomiting caused the parents to call their family doctor on December 27, 1949. The child had been ill about sixteen hours, and in addition to the abdominal pain and vomiting, appeared to have a common cold.

He was admitted to hospital as a probable case of acute appendicitis. He was diagnosed to be suffering from an acute abdomen and an early pneumonia of the right lower lung.

Operation was performed. The appendix was normal. A cyst of the ileum, about the size of an orange, was found. Inflammatory reaction had bound down the distal loop of the ileum, producing an acute obstruction.

Because of the chest complication in this case, resection of the cyst was not carried out. The cyst wall was partially resected, the intestinal obstruction relieved, and the patient was speedily returned to the ward.

The right lung pneumonia was treated medically. Collapse of the lower lobe of the left lung occurred. This condition cleared on medical treatment and the child was discharged on January 13, 1950. Subsequent operation will probably be needed.

CASE II.—C. L., male, aged 3 years.

Home conditions, excellent.

Past health.—Good, except for one abdominal attack on December 20, 1948, with pain, diarrhœa and vomiting. Complete recovery in four days.

Present history.—On December 3, 1949, had abdominal pain with vomiting. Appeared better on December 4. Next day had more abdominal pain, and constipation with vomiting. Seen on the morning of December 6 by the family doctor, who diagnosed an acute abdomen.

Temperature 99° F., pulse 100, abdomen very distended and tympanitic on percussion; constipated, vomiting. P.R. examination gave no definite results. The child was very ill and toxic. The parents refused admission to hospital. An enema was given and some fluid and flatus passed but as his condition was deteriorating the parents agreed to hospital admission.

Appendicitis was thought to be the probable diagnosis. At 9.30 p.m. on December

6, an operation was performed. A large cystic swelling was found about 9 inches on the proximal side of the cæcum, producing an acute obstruction (*see* Fig. 1). The



FIG. 1.—The cyst.



FIG. 2.—Radiograph of cyst with catheter through ileum.

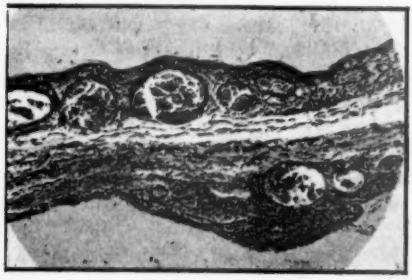


FIG. 3.—Low-power photomicrograph showing wall of small bowel above and cyst wall below; both are acutely inflamed and the essential features consequently indistinct. Both the bowel mucous membrane and the epithelium lining the cyst have disappeared and the smooth muscle coats have been broken up by the inflammatory process.

ileum appeared to encircle the cyst. A side-to-side anastomosis of the ileum was performed and the entire cyst and that section of the ileum encircling the cyst were removed.

A relatively uninterrupted recovery occurred, and the child was discharged from hospital on December 13, 1949.

On subsequently examining the cyst, I found that the ileum was stretched out on its surface and was closely adherent to it. To demonstrate this and in an attempt to establish the diagnosis I syringed normal saline through the section of ileum. The saline did not enter the cyst.

A solution of methylene-blue through the ileum from a syringe did not enter or stain the cyst.

I then passed a solution of sodium iodide in a similar way and had a radiograph taken.

A rubber catheter was then manipulated through the ileum and filled with sodium iodide solution for a radiograph (Fig. 2).

I next made a small incision into the ileum, to obtain a tiny piece of the ileum and the cyst walls for a histological section.

The pathologist reported that the cyst contained brownish jelly-like material and that a histological section of the external wall showed that the muscle coat of the ileum passed into the cyst wall (Fig. 3).

Thyrotoxicosis in a Newborn Infant.—B. M. MARGETTS, M.B., D.C.H. (for MARY J. WILMERS, M.D., M.R.C.P.).

C. G., male, aged 10 weeks.

History.—Normal birth at home. Maturity not definitely known as mother menstruated until eight weeks before delivery. Birth weight 5 lb. 13 oz. "Very skinny" and eyes seemed prominent. Always difficult over feeds. Bottle-fed. Rather lethargic at first. Developed diarrhœa and vomiting at 4 weeks and was admitted to hospital.

Family history.—Mother diagnosed as thyrotoxic one year ago but received no specific treatment. Was ill during last two months of pregnancy with swollen ankles and palpitations. Treated with phenobarbitone and digitalis by her doctor. One normal sister aged 21 months.

On examination (17.12.49).—Thin, restless infant. Weight 5 lb. 6½ oz. (at 4 weeks). Blinking infrequent. Palpebral fissure widened, and slight proptosis present. Thyroid gland *not* palpable. Skin warm but no excess sweating. Pulse rate 160–200.

Investigations.—E.C.G., 23.12.49: R. axis deviation. Amplitude normal for age. Rate 190 regular. 1.2.50: Rate 160 regular. Glucose tolerance curve normal. Blood cholesterol—140 mg. per 100 ml. X-rays: Epiphyses showed normal development for age. Chest gave no evidence of retrosternal goitre or thymic enlargement.

Progress.—No vomiting after admission. Loose green stools 4–8 daily continued for five days, since when stools normal. Feeds: Half-cream dried milk. Calories 65 per lb. (143 per kg.). Protein—6 grammes per kilo. Child has gained steadily. Weight at 10 weeks 8 lb. 4¾ oz.

The infant now (14.2.50) weighs 9 lb. 12 oz. (4·43 kilos) at the age of 3 months. Exophthalmos and hyperkinesis are diminished but still present. The tachycardia is also less, the pulse range being 135–160.

Comment.—The onset of the disease under the age of 1 year is extremely rare. There are references to only 6 true cases in the literature. The notable feature of the published cases, apart from that reported by White (1912), which died at 3 days from cerebral hæmorrhage, is the benign course. One case had proptosis at the age of 4½ months and had symptoms of mild thyrotoxicosis at the age of 14 years (Ellis, 1935). No treatment was undertaken other than the administration of Lugol's iodine. Another case (Elliot, 1935), a child aged 6 months, developed signs of hypothyroidism following partial thyroidectomy. It seems, therefore, that in the presence of adequate weight gain and normal heart rhythm and in the absence of persistent diarrhœa no treatment is indicated. It is not clear yet whether the condition of the infant is a passive result of untreated thyrotoxicosis in the mother or is due to active hyperthyroidism.

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Miliary Tuberculosis Controlled with Streptomycin and Promizole.—EVELYN WATKINS, M.B. (for E. HINDEN, M.D., M.R.C.P.).

C., male, aged 5½ months.

28.9.49 : Admitted to Plaistow Fever Hospital at request of local Chest Clinic. Father had died of phthisis some weeks previously; mother died of post-partum hæmorrhage and post-mortem showed active pulmonary tuberculosis. The child's

chest X-ray showed bilateral mottling. He had been refusing feeds and losing weight for five weeks.

On examination.—Condition poor, marked wasting. Weight 12 lb. Harsh cough, chest expansion poor; bronchial breathing below angle of right scapula. Spleen just palpable. Further investigations showed a positive tuberculin patch test, chest X-ray typical of miliary tuberculosis, and very many acid-fast bacilli in the stomach washouts. Repeated examinations of C.S.F. failed to produce evidence of meningitis.

Treatment.—Intramuscular streptomycin for 120 days; sulphetrone for two weeks, replaced by promizole from July 30 (when this drug became available through the kindness of Prof. Edith Lincoln of New York). Dose at first 0·25 gramme six-hourly, later adjusted according to blood levels. Given extra vitamins, iron, and on one occasion a blood transfusion.

Progress.—Poor at first. Cough and vomiting persisted for eight weeks, a low fever for twelve weeks. At the end of ten weeks (i.e. after six weeks of promizole) his weight had dropped to 11 lb. and Hb to 52% (from 72%). Thereafter improvement set in and has been steadily maintained but for a recent cold; his weight is now 17 lb. Radiologically there has been little change till the last picture (Jan. 16) which, after seven months, shows some clearing of both lungs, the left more than the right.

[*February* 24, 1950]

Electrolytic Misadventures in Infancy

PRESIDENT'S ADDRESS

By W. W. Payne, M.B., M.R.C.P.

To enable one to consider changes which occur in the living child it is necessary to compose a hypothetical normal and to ascribe values to the various physical and chemical states. In the normal healthy infant these states are not constant but vary to a greater or lesser extent around a mean—this mean value is the so-called normal and is usually quite easy to discover—the range of the variations compatible with good health is, however, far from easy to determine (Tables I and II; Fig. 1).

Table I.—Approximate Values of Some of the Fluid Relationships of a Hypothetical Normal Infant of 7 kg.

Plasma volume	350 c.c.
Interstitial fluid	1,050 c.c.
Intracellular fluid	3,500 c.c.
Daily Water Loss	
Urine	600 c.c.
Skin and lungs	200 c.c.
Fæces	50 c.c.
Total intestinal secretions	800 c.c.

Table II.—Acid-base Composition of Blood Plasma

Base mM/L.		Acid mM/L.	
$Na^{\cdot}$	142	HCO'_3	27
$K^{\cdot}$	5	Cl'	103
$Ca^{\cdot\cdot}$	5	HPO''_4	2
$Mg^{\cdot\cdot}$	3	SO''_4	1
	—	Org. Ac.	6
	155	Protein	16
			155

The main ways in which departure from the normal occurs are: (1) Alteration in osmotic pressure. (2) Alteration in hydrogen-ion concentration. (3) Alterations in chemical composition, apart from the effects of (1) and (2).

The osmotic pressure is affected by loss or gain of water or by loss or gain of salts. Loss or gain of water and salt in isotonic solution, while altering the fluid balance will not alter the osmotic pressure, thus the very considerable changes of shock from burns or bleeding are usually not associated with any change in the osmotic pressure.

Table I and Fig. 1 show how water alone or water and salts in isotonic strength may be lost from the body. The physico-chemical result may be quite different but the clinical term used to describe these changes is the same for both—"dehydration." If one could only coin convenient terms to describe the quite separate physico-chemical changes the existence of different clinical pictures of each condition would be much more easily appreciated. The only terms in use are anhydræmia (McCance) and hyperelectrolyteæmia (Rappaport) to describe increased osmotic pressure. Most of the symptoms of "clinical dehydration" are not due to true dehydration but to loss of isotonic fluids. The opposite side of the picture—too much water, "hypo-electrolyteæmia"—has no other name but forms part of the picture of salt depletion and Addison's disease, and too much isotonic fluid in its more marked state is described by its commonest symptom—œdema.

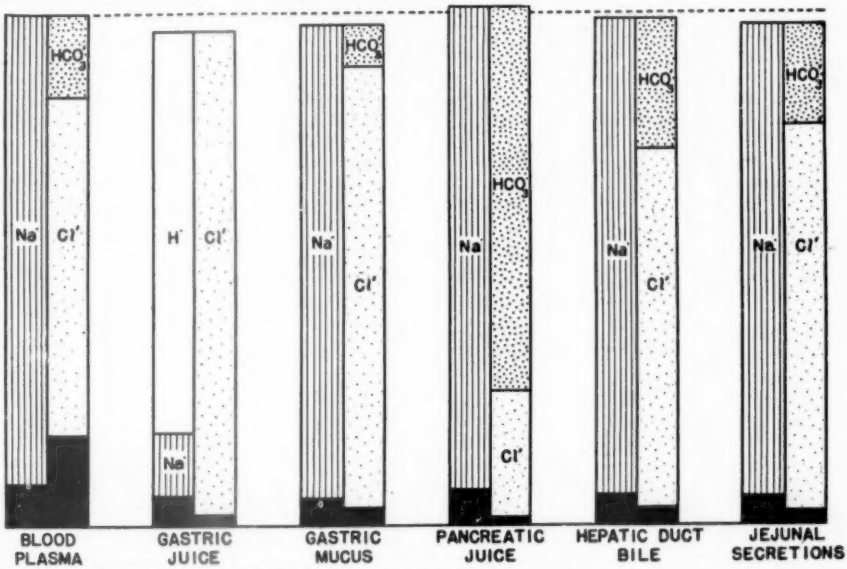


FIG. 1.—Electrolyte composition of gastro-intestinal secretions. The relative amounts of sodium, chloride, and bicarbonate ion in the digestive secretions are shown. The sums of the other anion and cation components are indicated, in black, at the foot of their respective columns.

Alteration of the hydrogen-ion concentration may be due to addition or loss to the body of alkaline or acid salts, to the compensating changes in the body due to attempts to minimize the damage caused by alteration of the osmotic pressure, or to the production of organic acids, examples of which will be seen occurring in the cases following.

Alterations in the chemistry cover a very wide subject but I am only considering changes in potassium and calcium—the changes in Na and Cl may produce effects of a purely chemical character but the physical changes are so great that it is not possible to distinguish them.

Hyper-electrolyteæmia

The first group of cases show a marked increase in electrolyte concentration from different causes.

Case I (Table III).—J. M., male, aged 6 months, developed gastro-enteritis in a babies' home in the country. Three days later he was transferred to the local hospital and given several intravenous drip transfusions. Vomiting and diarrhœa persisted and on the eighteenth day of his illness he was transferred to the Hospital for Sick Children, Great Ormond Street.

Condition on admission.—Sunken eyes, grey complexion, slight loss of skin turgor (more marked on the front of the thorax), œdema of legs, back and lungs and rapid respiration. The chemistry shows gross hæmo-concentration and, calculated by difference, a marked acidosis. There must have been: (1) Failure to give enough water. (2) Failure to replace the base lost in the stool.

TABLE III.—CASE I

Day	1	2	3	4
Cl mM/L.	177	108	118	105
CO_2 mM/L. ..	—	35	—	26·6
Na mM/L.	210	174	166	152
K mM/L.	3·2	3·4	4·7	5·8
Hb%	140	105	105	100

Case II (Table IV).—B. A., boy, aged 1 month, admitted with twenty-four hours' history of illness—a not very marked diarrhœa and no vomiting, but refusal of foods. (The mother gave a very poor history.)

Condition on admission.—He was collapsed, cold and slightly cyanosed. Some oscillating fluttering movements of eyes and eyelids were seen. There was no "dehydration". The respiration was rapid. The C.S.F. was examined and showed a very high chloride, sugar and urea content. Examination of the blood confirmed these values and he was given intravenous sodium lactate and later Hartmann's solution and 5% glucose. Some insulin was given subcutaneously. He developed œdema while still not fully rehydrated. His symptoms steadily improved and he became physically normal, but he showed marked mental deterioration, taking no notice of anything and sucking poorly. He has slowly improved and at 2 years his mentality is within normal limits. The cause of the catastrophe is not apparent; possibly there were some C.N.S. changes affecting the osmo-regulating centre, as the gross abnormalities found could not have been caused by the twenty-four hours' illness—in particular so high a blood urea would not occur even after five to seven days' anuria.

TABLE IV.—CASE II

Day	1	3	5	7
Cl mM/L.	153	105	104	—
CO_2 mM/L. ..	6·5	26·3	—	—
Na mM/L. ..	187	—	—	—
Urea mg.% ..	465	238	72	23
Sugar mg.% ..	458	78	70	—
Ca mg.%	7·8	—	6·5	—

Case III (Table V).—C. W., girl, aged 8 months. Under treatment in hospital for renal acidosis (nephrocalcinosis); sent home on a high dose of alkali. An unfortunate error was made and she was given a much higher and more cencentrated dose of alkali than she should have had, for some thirty-six to forty-eight hours. There had been some vomiting and diarrhœa.

Condition on admission.—She was "dehydrated" with cyanosis and feeble respiration. She was having frequent convulsions with extended arms and legs and arched back, and between attacks there was conjugate deviation of the eyes. There was no neck rigidity and the fontanelle was depressed. After treatment with 5% glucose and then glucose saline intravenously she became œdematous but ultimately physical recovery occurred. There was, however, a considerable degree of damage to the C.N.S. and the conjugate deviation of the eyes persisted for two to three weeks. At the end of four months there was a slow but steady improvement but she is still mentally retarded. Here there was no doubt as to the cause—alkalosis and increased osmotic pressure.

TABLE V.—CASE III

Day	1	2	3	4
Cl mM/L.	128·5	92	93	108·5
CO_2 mM/L. ..	49·5	34·4	34	28
Na mM/L.	—	157	149	—
K mM/L.	—	—	2·7	4·0
Ca mg.%	7·6	—	7·6	8·3
Sugar mg.% ..	296	153	—	79
Urea mg.% ..	—	74	50	20

In all these three cases and in others we have seen, the skin had lost its normal elasticity but it was not like the thin inelastic skin of the usual clinical dehydration—it was thicker, so much so that in some cases it has resembled scleroderma, in others it was more like perished rubber.

In several cases there have been C.N.S. symptoms and lumbar puncture has been performed before the condition has been diagnosed. Convulsions and localized twitching and eye movements occur and the infant relapses easily into a semi-comatose state.

Œdema is an early symptom in some—in the rest it occurs as soon as treatment is started. The presence of apparent dehydration and œdema is a striking feature. The condition in some cases is secondary to gastro-enteritis or some obvious cause but others occur acutely with too short a history to account for so great a chemical change.

Hypo-electrolyteæmia

Case IV (Table VI).—A boy, aged 5 months, had had gastro-enteritis for three to four weeks and was steadily improving. He started vomiting again and rapidly became clinically dehydrated. It will be seen that the plasma Cl and Na are low. K varied with therapy and was not abnormal enough to be a factor in the symptoms. After seven days on eucortone he was able to maintain his NaCl level unaided. At no time was there any evidence of a low renal threshold for Cl.

TABLE VI.—CASE IV

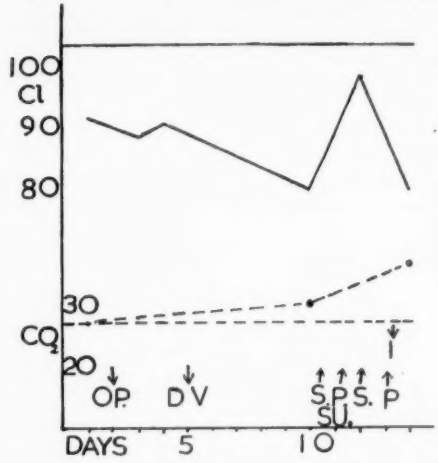
Day	Cl mM/L.	CO_2 mM/L.	Na mM/L.	K mM/L.	Treatment
1	89·5	19·6	—	4·0	KCl in feeds
8	83	23·3	122	6·7	
9	105	—	—	—	Saline intravenously
10	90	17·7	—	4·8	Eucortone
12	97	18	141	3·1	

Many similar cases have been observed. In only one was a low renal threshold found. The effect of Doca and of cortical extracts has been variable—in some cases there has been no effect and repeated saline infusions or extra salt by mouth have been necessary. Ultimate recovery with ability to maintain a normal NaCl level has been invariable in those that survived.

Case V (Table VII).—Male, aged 1 month, had been in hospital for three weeks with urinary tract obstruction. At first the blood urea was constantly over 150 mg.% but after suprapubic cystotomy it fell to 90 mg.%. He was beginning to recover and was taking feeds well. He suddenly became dehydrated and collapsed with rapid respiration and the blood Cl was very low. He was given saline and later Hartmann's solution with some improvement in Cl level. It was noticed about this time that his respirations were even more rapid and he was still extremely collapsed. It had not been considered likely with so low a Cl that he would be acidotic but the high respiration rate suggested this possibility and the blood showed on examination an extreme acidosis. He improved on being given M/6 sodium lactate but the Cl fell again. Ultimately the Cl was raised to normal level. Unfortunately the NaCl was not estimated in the urine so the existence of a temporarily reduced renal threshold could only be conjectured, but was not unlikely in view of the grave renal damage. He had had a low intake of salt as he was not taking his feeds well and he had some polyuria with the high blood urea. The collapse was probably of the same type as is common in Addison's disease.

TABLE VII.—CASE V

Day	Cl mM/L.	CO_2 mM/L.	Urea mg.%	Clinical notes and treatment
1	83	—	154	Plasma and whole blood intravenously
2	—	—	—	Sudden collapse Glucose saline intravenously
3	91	—	113	Respiration rate rapid
5	98	—	98	Hartmann's solution intravenously
6	—	—	—	" " "
7	93	—	94	Respiration rate increasing
8	88	9·8	106	
9	—	—	—	1/6 Molar sodium lactate intravenously
10	79	—	93	
12	83	—	—	Œdematous. Respiration normal. Taking fluids by mouth
20	104	—	45	Improving



Case VI (Fig. 2).—R. H., male aged 5 months, was admitted with vomiting and diagnosed as having a partial obstruction of the duodenum—at operation it was found to be due to a band. Three days after the operation he developed diarrhœa and vomiting. After a few days bowel movements ceased and duodenal suction was started but he died before gut movements were re-established. All blood examinations showed a low electrolyte level—due to the vomiting. In contrast to Case V, this boy had an alkalosis due at first to the vomiting and later to the treatment.

FIG. 2.—S.=Saline intravenously. P.=Plasma intravenously. S.U.=Gastric suction. Horizontal lines=Normal levels.

There is no clear-cut symptomatology in these cases of hypo-electrolyteæmia except the liability to sudden collapse and a tendency to vomit.

Alkalosis

Probably the most common cause of alkalosis in children is hypertrophic pyloric stenosis. It is almost the only condition in which persistent vomiting is associated with hunger and where therefore there is a constant outpouring and loss of acid gastric secretion. Table VIII shows 2 very advanced cases taken from my earlier

TABLE VIII.—TWO CASES OF PYLORIC STENOSIS

	Isotonic	Hypotonic
Cl mM/L.	84	54
CO_2 mM/L.	46	43

records. They have been selected to show a simple alkalosis and an alkalosis combined with hypo-electrolyteæmia—a very dangerous combination. In these cases there are three separate factors—the loss of isotonic acid gastro-secretion, the loss of base in the urine in an attempt to correct the acid-base balance and, owing to the vomiting preventing absorption, a loss of water. These three variable factors cause the differences in the clinical picture. The degree of clinical dehydration is not therefore proportional to the degree of alkalosis or of salt loss. The liability to collapse depends both on the hypo-electrolyteæmia and on the alkalosis; the latter can usually be detected by the altered respiration which may be shallow, irregular or, less commonly, slow.

Case VII (Table IX).—J. G., male aged 8 months, admitted for operation on a hare lip, subsequently developed gastro-enteritis with a rapid rise of temperature and cyanosis. He was put in an oxygen tent and given sulphonamides as well as the routine gastro-enteritis treatment. He improved, but on oral feeding being restarted he vomited again. To check this, residual stomach washouts were performed for two days and intravenous plasma given, but the vomiting continued and he became œdematous. At this point he was found to be alkalotic and oral HCl was given. Ultimately he recovered completely.

TABLE IX.—CASE VII

Day	Cl mM/L.	CO_2 mM/L.	Ca mg.%	Comment
1	—	—	—	Sulphonamides and alkali
2	94	24·5	—	
3	—	—	—	Vomiting. Frequent stomach washouts
4				Intravenous plasma
5	77	37·5	8·0	Hydrochloric acid added to feeds
6	97	—	—	

There are two sources of alkali here, and in all probability neither would be sufficient alone to cause alkalosis. They are: (1) Alkali given as a routine with sulphonamides (Mist. Pot. Cit. Alk. ℥ i × 5, equivalent to 42 grains (2·72 grammes) $NaHCO_3$ a day). (2) The citrated plasma which contains the equivalent of 25 grains (1·62 grammes) $NaHCO_3$ per pint. The stomach washouts might also have caused loss of acid.

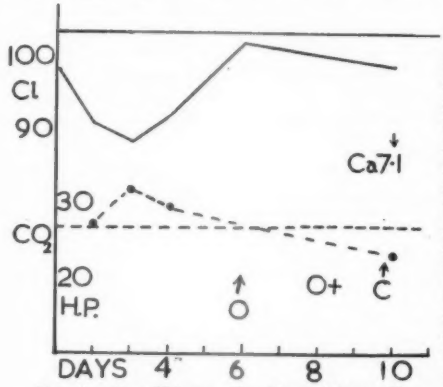


FIG. 3.—O.=Œdema. C.=Convulsions. H.=Hartmann's solution. P.=Plasma. Horizontal lines=Normal levels.

Case VIII (Fig. 3).—R. C., male aged 7 weeks, admitted with ten days' history of gastro-enteritis which had been vigorously but unsuccessfully treated before admission. He was wasted and dehydrated with cyanosed extremities and very shallow respirations. He was given the usual intravenous treatment, using half-strength Hartmann's solution and plasma alternately. It will be seen that the initial Cl was a low normal[1] and that subsequently alkalosis developed which was corrected. The child then became œdematous, later had convulsions and the calcium was found to be low. Correcting the alkalosis alone was sufficient to enable the calcium to right itself—no extra Ca was given. This is again a part of the picture of the reaction to the acute phase according to Rappaport, but it has been very rare at Great Ormond Street.

Acute Acidosis

There are many causes for acute acidosis in infancy. The two main types are: (1) That due to the disturbed electrolyte balance. (2) That due to excess production of acid end-products of metabolism.

Case IX (Table X).—Female aged 10 weeks, admitted with a three-day history of acute gastro-enteritis; she was clinically dehydrated. She responded to the usual treatment and made a rapid and uneventful recovery. The acidosis was due to loss of base. Hyper-electrolyteæmia is also present.

TABLE X.—CASE IX

Cl mM/L.	133
CO_2 mM/L.	14
K mM/L.	6·5
Na mM/L.	179
Sugar mg.%	136

Case X (Table XI).—Female aged 4 months, admitted three weeks previously with gastro-enteritis and evidence of parenteral infection. Treated with sulphonamides and the usual intravenous measures and was slowly improving. A sudden relapse occurred with diarrhœa and vomiting, collapse, and sunken eyes but only a moderate degree of clinical dehydration. The urine contained acetone. Note the low chloride and bicarbonate with a normal sodium indicating that the acidosis was due to retention of acid end-products of metabolism. The ultimate result after bilateral myringotomy was satisfactory.

TABLE XI.—CASE X

Day	1	4	6
Plasma chlorides mM/L.	88	102	103
„ bicarbonate mM/L.	15	20·4	—
„ sodium mM/L.	144	—	143
„ potassium mM/L.	5·9	5·1	4·75
„ protein %	7·8	7·6	7·7
„ urea mg.%	42	—	13
Hæmoglobin %	91	105	82
Urine acetone	++	tr	tr

[1]The initial routine treatment assumes an acidosis—when this is not present, as in this case which had already had some treatment and had passed the acidosis phase, an alkalosis may easily be produced. Rappaport considers the alkalosis to be a reactive phase to the acidosis but I think it is an indication of over-treatment as it was here.

Calcium

Case XI (Table XII).—A. F., female aged 3 months, admitted with one day's history of illness. She had always been difficult with her feeds but on the day before admission she refused all feeds and developed a high-pitched scream—later on she showed a rapid oscillatory movement of the eyes and twitchings of the arms and legs but no diarrhœa and vomiting. She was collapsed and cyanosed with moderate dehydration. The lower limbs were stiff but there was no neck rigidity. The initial chemistry did not show a sufficient degree of hyper-electrolyteæmia to account for the symptoms. Ca was estimated and revealed the cause. The fluid balance was restored and Ca given with only slight effect on the Ca level. Œdema developed to such a degree that the child died of pulmonary œdema. There was no post-mortem examination. The cause of the low Ca remains a mystery as do most of the other recorded cases of spontaneous tetany in infancy. The cause of the electrolytic imbalance is also not clear.

TABLE XII.—CASE XI

Day	1	3	4	5
Cl mM/L.	—	131	120	111
CO_2 mM/L. ..	—	—	23·5	—
Na mM/L.	—	—	162	—
Ca mg.%	—	4·6	5·0	—
Urea mg.% ..	—	320	256	—
Sugar mg.% ..	270	162	120	—

Potassium

The importance of potassium in the tissues and blood has been given prominence by Darrow's work. In early acute acidosis the potassium is increased sufficiently in some cases to cause alteration in the electrocardiogram.

Table XIII shows two examples of the blood picture in the acute stage to illustrate this.

TABLE XIII

Case P	Day 1	Day 5	Case S	Day 1	Day 15
Chloride mM/L.	123	106	Chloride mM/L.	144	114
Sodium mM/L.	171	152	Potassium mM/L. ..	7·9	5·6
Potassium mM/L. ..	7·3	5·0	Protein %..	6·7	5·8
Protein %..	7·0	4·9	Urea mg.%	211	30
Urea mg.%	44	17			

With such high values it is dangerous to give potassium in the intravenous fluid. In the post-acidotic phase when recovery is delayed the loss of potassium which occurred during the acute phase may prevent the rebuilding of the tissues and giving KCl in the drip or by mouth has unquestionably improved the results.

Table XIV shows a typical case in which no potassium has been given.

TABLE XIV

Day	1	4	12
Chloride mM/L.	119	104	111
Bicarbonate mM/L.	10	26	—
Sodium mM/L.	—	138	155
Potassium mM/L.	4·2	3·4	1·6
Protein	—	4·5	3·6
Urea mg.%	22	24	12

I would like to thank the various members of the Staff of the Hospital for Sick Children, Great Ormond Street, for allowing me to quote cases under their care and in particular Dr. B. Schlesinger who, as Physician in charge of the Gastro-enteritis Ward, has had the management of the majority of these cases.

Section of Psychiatry

President—W. J. T. KIMBER, D.P.M.

[*March* 14, 1950]

DISCUSSION ON SOME SOMATIC ASPECTS OF SCHIZOPHRENIA

Dr. F. Mackenzie Shattock: It is usual to introduce a discussion by a brief reference to what is already generally accepted and then from this common ground to pass on to what is still controversial. But there is unfortunately very little agreement on any of the somatic aspects of schizophrenic illness, and this is the more surprising as these physical manifestations are mentioned in every textbook of mental illness and numerous articles have been published on the subject. There is no agreement on their significance, their nature, their number, the frequency of their occurrence, nor on their response to treatment, and it would be fair to say that the most constant feature in their descriptions is the insistence on their variability. If one were tempted by this conclusion to regard them as incidental, and therefore as unimportant, one would run counter to what is accepted in somatic medicine. It would probably be wiser to attempt to relate their variability to the interplay of numerous factors which determine the clinical syndrome.

To introduce the discussion, I should like to refer to observations made in the course of a longitudinal study of 600 psychotics, both early and chronic cases of mental illness (Shattock, 1950). An equal number of schizophrenics and non-schizophrenics were observed, the latter included patients who suffered from an affective mental illness, mainly depressives, and a group of aments and dements. There were many deteriorated schizophrenics among the dements, and this may account for the fact that the incidence of physical abnormalities, which was highest in schizophrenics and lowest in patients who suffered from an affective illness, was intermediate in the group of dements and aments.

A diagnosis of schizophrenia was based on the consensus of clinical opinions expressed in the case-sheet, and was aided by information on the patient's history and on the course of his clinical illness. An attempt was made to subdivide schizophrenic patients into the usual clinical subgroups, but this only succeeded in separating catatonic from paranoid cases and it was often necessary to reclassify patients who were observed over four years.

The physical signs about to be described were most common in catatonic patients. They were rarer in paranoid schizophrenics, rarer still in patients suffering from an affective illness, and were not encountered in the few well-preserved paranoics who came under observation. These physical signs are definite and unmistakable, but they are not irreversible, and should be regarded as manifestations of disturbed function rather than as pathological lesions in the ordinary sense of the word. The few irreversible signs which were encountered were probably all secondary to prolonged dysfunction, for instance changes in the integument after prolonged vascular deprivation, and evidence of persisting dysfunction of the liver in patients who had entered on a good clinical remission.

THE PERIPHERAL VASCULAR DISTURBANCE

This is the change which is most frequently mentioned in the literature, probably because it is so common and striking. In the patients observed, peripheral cyanosis was three times more common among schizophrenics than among affective psychotics. When the ward temperature was between 62° and 65° F. (16·7°–18·3° C.), 63% of the schizophrenic women showed some discoloration of their extremities. Cyanosis was severe in up to 16% of these patients and in the worst cases the feet and the lower half of the legs, more rarely the hands, were of a dark blue or plum colour. The face, body wall, and especially the breasts were also discoloured in a number of cases. Male schizophrenics, who wore heavier clothing than female patients, were less frequently affected, but cyanosis of their extremities could easily be provoked by exposing their forearms and legs below the knees for half an hour to ordinary room temperature. Raising the room temperature for one hour to 82° F. (27·7° C.), a relatively high indoor temperature, did not usually relieve peripheral cyanosis, but cyanosis could be prevented by wrapping the patients' limbs in cotton-wool before the room temperature was lowered.

It was always possible to afford relief, even to the worst cases, by securing efficient vasodilatation of the peripheral vessels. This could be achieved in a variety of ways, most

simply by warming the patient's body with an electric cradle, but also by " reflex hyperæmia", warming an " indifferent " limb in a water bath, provided the bath was constantly refilled after the cold cyanosed limb had been immersed; by "passive hyperæmia", following temporary occlusion of the main limb vessel with a tourniquet; by administering a vasodilator drug, such as nicotinic acid, and by blocking the nerves which carry vasoconstrictor fibres to the extremities.

Of greater clinical interest is the relief of cyanosis which coincides with a clinical remission. It is possible to time the onset of these physical and mental events with some precision in catatonic patients who experience a brief clinical remission two or three hours after electroconvulsion. When a previously mute and resistive cyanosed patient became co-operative and uttered a few amiable sentences, either before or shortly after rising from the treatment couch, it was usual to find that his limbs had assumed a normal appearance. This they retained as long as the mental remission lasted, but with the onset of a mental relapse, frequently only a few days later, cyanosis of the extremities was quite as evident as before the brief remission. This sequence was witnessed on many occasions, and in some patients the colour of the extremities could be regarded as a faithful indicator of their temporary mental state. In patients whose mental condition showed no improvement after electroconvulsion there was no detectable change in the peripheral vascular condition.

The improvement in the peripheral circulation, following vasodilatation, can be estimated

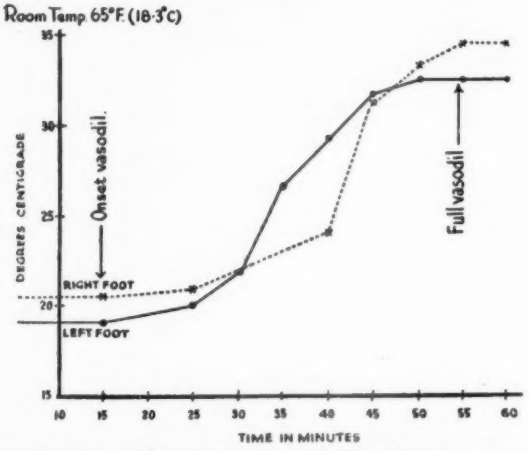


CHART I.—Reflex vasodilatation. Foot temperature (1st cleft) before and after immersion of left forearm in water bath 45° C. (113° F.).

E. S., aged 46. Hebephrenic schizophrenic. Cyanosed extremities. Limb arteries normal on palpation. Fifteen minutes' delay before onset of vasodilatation.

by the rise in the peripheral surface temperature. Chart I illustrates this change, which was observed in a schizophrenic with cyanosed extremities, following "reflex vasodilatation". The response is similar to that of a normal person, but it is often delayed, in this case by fifteen minutes, is usually much more gradual than in persons whose extremities are not cyanosed, and spreads slowly from the proximal to the distal part of the limb instead of occurring almost simultaneously over its whole surface.

Chart II (A and B) illustrates a similar change following electroconvulsion. This patient, a stubborn resistive catatonic, had not responded to the first 8 treatments, and in spite of daily convulsions her limbs remained deeply cyanosed. Chart II (A) shows a low foot temperature on the eighth day, and a minimal rise of temperature after thirty-five minutes' warming of an indifferent limb. On the following day, after the ninth electroconvulsion, the patient's mental condition showed a striking change and for the first time she spoke freely, in a rational, sarcastic way. Her limbs had a normal appearance; the brachial and dorsalis pedis arteries, which had been cord-like and pulseless, were now quite normal; the foot temperature had risen from the original temperature of 22° to 34° C. (71·6°–93·2° F.), and rose a further two degrees after "reflex vasodilatation".

Improvement of the peripheral circulation was also noted in patients who had experienced a spontaneous remission and in those whose mental and bodily condition had improved more gradually during a course of insulin comas, but in neither case was it possible to time

the coincidence of these changes with the same accuracy as was possible after electroconvulsion.

It would be reasonable to ascribe improvement in the peripheral circulation, after a remission, to an increase in the patient's physical activity, but this suggestion is not supported by the following considerations:

(*a*) There is a poor correspondence between a patient's physical activity and cyanosis of his extremities. Restless patients are among the worst sufferers, and when restlessness decreases with mental improvement, the improvement in the peripheral circulation is often noticeable.

(*b*) Severe physical exercise does not as a rule relieve these peripheral vascular disturbances and in some cases causes further deterioration.

(*c*) A few immobile catatonics and many affective psychotics, who sit almost immobile, show no vascular abnormalities of their limbs.

Further points of interest noted were:

(*a*) The significantly lower average surface temperature of cyanosed limbs; the significantly lower peripheral temperature of female psychotics compared with male psychotics, and of female schizophrenics compared with female affective patients.

(*b*) Young schizophrenics, during the first months of their illness, may show some vasomotor instability which causes their hands to assume a cyanotic colour when they are

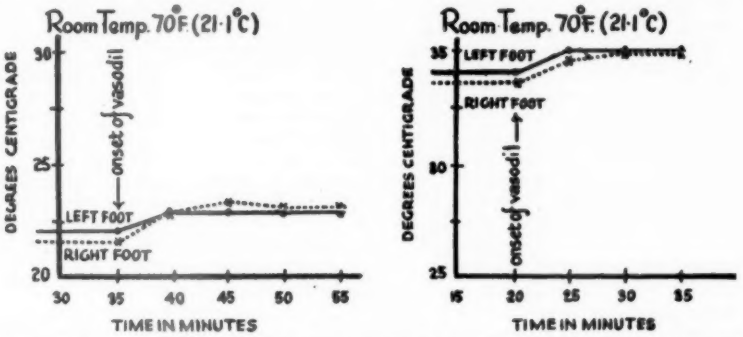


CHART II.—Reflex vasodilatation. Foot temperature (1st cleft) before and after immersion of left forearm in water bath 45° C. (113° F.).

A.—4.7.45: Before remission. M. K., aged 25; catatonic schizophrenic. Stubborn and irrational. Cyanosed extremities. Cord-like pulseless brachial and dorsalis pedis arteries. Thirty-five minutes' delay before onset of slight reflex vasodilatation.

B.—5.7.45: On day of remission. M. K., six hours after ninth E.C.T., which initiated a remission. Rational, sarcastic, suspicious. Extremities not cyanosed. Vessels normal. Twenty minutes' delay before onset of reflex vasodilatation.

emotionally disturbed, as for instance by a reference to their particular difficulties. This psychosomatic response differs from the exaggerated response to chilling, which has already been described, although both are evidently dependent on vasoconstrictor reactions. The response to chilling of schizophrenic patients is similar to that of cold-sensitive persons, so fully investigated by Sir Thomas Lewis (1936). These cold-sensitive subjects and schizophrenics respond to a fall in external temperature which does not seriously affect the peripheral circulation of less sensitive persons by excessive vasoconstriction, peripheral cyanosis and chilblains, and in extreme cases by gangrene of the digits.

The Condition of the Limb Vessels of Patients Who Suffer from Severe Peripheral Cyanosis

The main arteries of the limbs of these patients are sometimes firmly contracted, cord-like and pulseless. The brachial artery was not infrequently found to be pulseless, but the axillary artery was always normal and a faint pulse could usually be felt at the wrist. The arteries of the lower limbs were sometimes also contracted below the level of the popliteal vessel, which was always normal. When the dorsalis pedis artery was contracted, it could be palpated and rolled under the skin.

In patients who had pulseless brachial vessels, a systolic reading could only be taken by obliteration of the radial pulse, since no sounds were audible at the elbow, or only a click or two when the cuff was deflated. A pressure of about 70 mm.Hg might suffice to obliterate the radial pulse and one could only speculate whether this represented a systolic reading,

or whether it merely reflected a change in the vessel wall. It is impressive to feel the change in one of these cord-like vessels, particularly in the brachial artery, when it softens, dilates and begins to pulsate, while an indifferent limb is being warmed in a water bath. The same changes were observed in the vessels of patients whose extreme vasoconstriction was relieved by the onset of a remission, but the exact moment at which these spontaneous changes occurred was never witnessed.

The contracted vessels of the extremities could always be dilated, even when gangrene was already threatening the digits. Two patients were discovered in this condition and in both cases the toes were saved, with the loss of only a few flakes of skin, after the patients' bodies had been warmed with an electric cradle during two or three days. One of these patients died a year later from an intercurrent illness, and the vessels of her limbs, down to the smallest cutaneous vessels, were found on histological examination to be quite normal.

Schizophrenic patients who have a low blood pressure usually show a considerable rise in their systolic and pulse pressure after the onset of a remission. It was noted that the administration of sodium chloride or of desoxycorticosterone acetate also raised the blood pressure of these patients and was sometimes followed by striking physical and mental improvement.

In a survey of 550 female psychotics the lowest blood pressure readings were almost invariably found to be those of resistive difficult schizophrenics. Their average blood pressure was significantly lower than that of socialized or remitted patients, whereas no significant difference distinguished the blood pressure readings of the so-called refractory from those of socialized non-schizophrenic patients.

The Retinal Vessels in Schizophrenia

Ophthalmoscopic examination of 200 psychotics revealed that the retinal arteries of schizophrenic patients are often tenuous and that a segment of these vessels is sometimes temporarily occluded. These observations confirm the work of Cotton *et al.* (1940), who actually measured the calibre of the retinal vascular tree and found it diminished in schizophrenia. It is easy to restore contracted retinal vessels to their normal size by asking the patient to inhale for a few minutes a mixture of carbon dioxide and oxygen, an excellent cerebral vasodilator. It was interesting to note that many mute and resistive schizophrenics experienced a miniature remission immediately after these inhalations. They conversed freely for a few moments or a few hours, but no permanent benefit was derived by any of the patients who were observed.

The Change in the Metabolic Level

By plotting the peripheral surface temperature of a great number of individuals against their metabolic rate, Sheard and Williams (1940) have demonstrated a constant and linear relation between these two variables. If their conclusions are accepted, the low average peripheral surface temperature of schizophrenics is an indication that the average metabolic level of these patients is greatly depressed. R. G. Hoskins (1932) has drawn the same conclusion from his extensive metabolic investigations of schizophrenics and he states that their average oxygen consumption is only 75% of the normal value.

My only contribution to the study of qualitative metabolic changes in schizophrenia is the observation that repeated attacks of ketonuria, which are not always related to a diminished intake of food, are common in catatonia. These attacks are not accompanied by glycosuria and they are terminated by the addition of a large supplement of glucose and small daily dose of insulin to a diet already rich in carbohydrates.

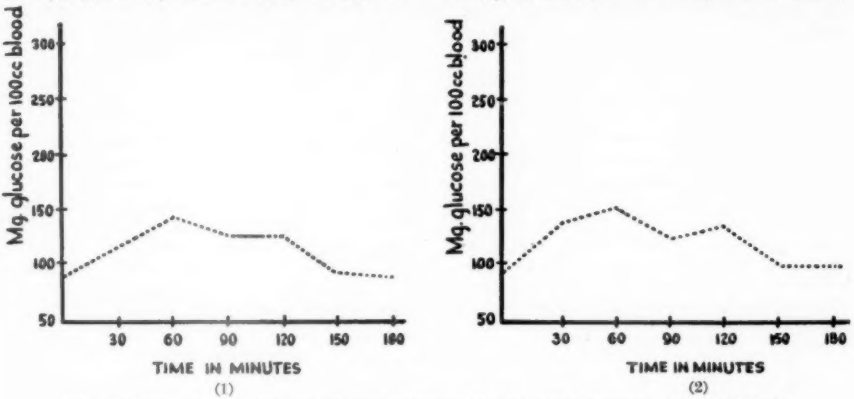
Carbohydrate Metabolism

No serious metabolic disturbance was revealed by repeated oral and intravenous glucose tolerance tests administered to 35 typical schizophrenics. The fasting blood sugar level of all these patients was invariably within low normal limits and only 5 of their number showed a slight prolongation of the hyperglycæmic curve. As 3 of these 5 patients were suffering from mild exophthalmos, their endocrine balance was probably disturbed. Protracted hyperglycæmia was the prerogative of emotionally disturbed affective patients and their O.G.T. curve sometimes showed a continuous rise over three hours after such trivial occurrences as an ill-timed announcement that a change to another ward might be necessary. Schizophrenics were quite immune from these psychological disturbances; their glucose tolerance curve was not appreciably altered by a change in their clinical status nor by the application of physical treatment.

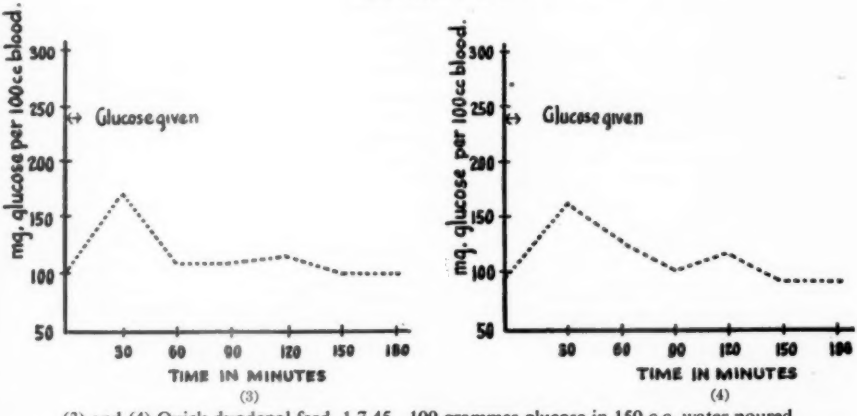
The rate of passage of food from the stomach into the duodenum must be taken into consideration when oral glucose tests are interpreted. It was found that after a glucose solution had been poured quickly into the small intestine, through a Miller-Abbott tube, a short sharp rise of the curve and a quick return to fasting level was the rule, whereas when the solution was poured in slowly a more sustained hyperglycæmic curve was obtained (*see* Chart III).

CHART III.

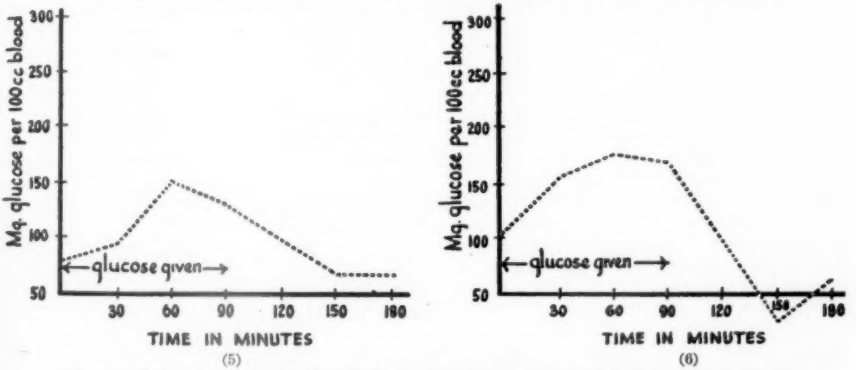
A.—(1), (3) and (5) Male schizophrenic, aged 26. B.—(2), (4) and (6) Male schizophrenic, aged 34.



(1) and (2) Graphs showing oral glucose tolerance, 9.7.45. 100 grammes glucose in 150 c.c. water given orally.



(3) and (4) Quick duodenal feed, 1.7.45. 100 grammes glucose in 150 c.c. water poured into small intestine at even rate in four minutes through a Miller-Abbott tube.



(5) and (6) Slow duodenal feed, 3.7.45. 100 grammes glucose in 150 c.c. water poured into small intestine at even rate in 90 mins. through a Miller-Abbott tube.

The urine of these patients was sugar and acetone free both before and after feeding with glucose.

Disturbance of Movement in Schizophrenia

It is perhaps not sufficiently recognized that catatonic akinesia is a disturbance of the waking hours, that the muscles of the catatonic relax during sleep and that movement is then free. While awake the catatonic may maintain a posture without fatigue, in spite of poor muscular tone, and like the hysteric he may clench his fists until contractures of the flexor tendons have developed. He may show no response to a painful stimulus, or merely a local withdrawal, although it is clear from his expression and from his memory of the event that he is fully aware of what is happening. There are features in catatonic limitation of movement which are reminiscent of the limitation of movement seen in post-encephalitic patients. In both cases movement is free when the patient is emotionally aroused, and in both cases convergence is difficult or impossible; the catatonic follows an approaching object by looking at it alternately with one or other eye. The disruption of ocular movements may also involve a dissociation of conjugate eye movements. One of the patients observed over some months sometimes combined a horizontal movement of one globe with a vertical or rotary movement of the other, a dissociation of conjugate eye movements which is rare in the adult, as it involves a disturbance of the fixation reflex acquired in the first months of life.

Disturbance of Endocrine Function

Only two of these disturbances will be briefly mentioned. The first is a disturbance of sexual function in female schizophrenics which has received little attention in the literature.

The vaginal mucous membrane of these patients was studied by the smear method of Papanicolaou (1933) in 30 young schizophrenic women. It showed an absence of normal cornification and an absence or marked diminution of glycogen in the cells, indicative of œstrogen deficiency. The appearance of the vaginal mucosa of 60% of these young women was characteristic of the menopause, and lesser changes were present in the others.

An incidental observation, for which no explanation can be offered, is the reinstatement of the menstrual cycle in patients in whom it had been absent for up to four years, after inhalation of a mixture of carbon dioxide and oxygen on two or more consecutive days. Once re-established the cycle continued in some cases over periods of two or three months, until it was again spontaneously interrupted.

Patients who suffer from the second endocrine disturbance show signs of adrenocortical dysfunction in various combinations. The clinical picture may resemble that of Addison's or of Simmonds' disease, with extreme asthenia, a dry atrophic or œdematous skin, a very low blood pressure and a slow heart, the pulse being sometimes as slow as 40, although there are no electrocardiographic abnormalities. A light brown or grey pigmentation of the trunk is common in female patients and much rarer in males. The nipples are often deeply pigmented, but the mucous membranes were never found to be affected. Hirsuties and a male type of body-hair distribution are also common in female patients and amenorrhœa is almost the rule. It is not easy to apply tests for adrenocortical function in patients who are seldom co-operative, but no evidence of dysfunction was obtained with the Robinson, Power and Kepler test, which measures delayed excretion of an additional intake of water.

Some of the asthenic patients recover spontaneously, but it is possible to hasten or even to initiate their recovery by the administration, over a few days, of a daily supplement of 5 to 15 grammes sodium chloride, or daily injection of Doca (10 mg. desoxycorticosterone acetate given daily for 2-3 days and reduced to 6 mg. daily or on alternate days, according to the observed rise of blood pressure, to the end of the second week). 8 patients who received these treatments were almost moribund when they were initiated; 2 of the 5 patients on Doca and one of the 3 receiving salt additions proceeded to a good physical and mental remission and were later discharged, the others showed physical but no mental improvement. The average blood pressure of these patients rose from 87 to 116 mm.Hg, and there was a significant rise in pulse pressure.

The polyglandular nature of the endocrine disturbance in schizophrenia suggests a pituitary rather than a primary adrenal dysfunction, and there is much collateral evidence to support this suggestion. Parsons (1949) and Pincus (1949) and their associates have noted that schizophrenics often fail to respond to psychogenic stresses by a fall in their lymphocyte count, although their response to strong stimuli, such as epinephrine and E.C.T., usually remains normal. This partial failure has been variously interpreted as evidence of hypothalamic unresponsiveness, as a sign of pituitary dysfunction, or as the result of primary adrenocortical failure. The same groups of workers have noted that psychotics may fail to show a normal lymphopenic response after they are exposed to a rise in environmental temperature, after exercise in an atmosphere of lowered oxygen concentration, or after an induced hyperglycæmia, but they found no unresponsiveness to adrenocortical steroids, when these were administered in adequate quantities.

Liver Function Tests in Schizophrenia

There are many contradictory claims in the literature on the presence or absence of liver damage in schizophrenia, and it is not often clear why the same test of liver function may give different results in the hands of various observers.

Three well-standardized flocculation tests were used on 300 psychotics, 100 schizophrenics, 100 patients suffering from an affective illness and 100 mixed psychotics suffering from senility, organic and epileptic mental illness. The technique employed was that used by Professor Maclagan (1947), who has been good enough to instruct us in the use of his serum colloidal gold, thymol turbidity and thymol flocculation tests. These tests were carried out by Mr. N. Warren, F.C.S., Senior Technician to Three Counties Hospital. A positive reaction to one or other of these tests is believed to indicate a rise in the gamma-globulin-fraction of the serum. This rise may have resulted from a disturbance of liver function, or as a response to various infections, or from changes induced by passive congestion and anoxia due to failure of the circulation.

An astonishingly high number of positive results were recorded in the 100 schizophrenics tested, one of the 3 flocculation tests being positive in as many as two-thirds of the female, and in one-half of the male patients. This incidence is even higher than that recorded by de Jong (1945) who used a different flocculation test on catatonic patients, and drew attention to the diagnostic value of these positive reactions in schizophrenic patients. Positive reactions to all 3 flocculation tests were given by 26% of the female, and 19% of the male schizophrenics. Among 200 non-schizophrenics there were only 12 patients (6%) who gave a positive reaction to one of the 3 tests, approximately the same incidence as in the general population, and 3 of these 12 positive reactors gave a history of previous attacks of infective jaundice or cholelithiasis.

It was not found possible to correlate positive reactions to flocculation tests in schizophrenic patients with characteristic forms of the clinical illness, but the majority of patients who gave these reactions were chronic cases, or patients who had entered on a remission after a severe schizophrenic illness.

If malnutrition, at some stage of a schizophrenic illness, were the main or only cause of liver dysfunction in these patients, one would expect to find a greater number of positive flocculation tests in senile and chronic depressive patients, who are also frequently ill-nourished. It is possible that schizophrenics suffer from a disturbance of liver function caused by stagnation and anoxia. The persistence of positive tests in patients who have entered on a good clinical remission may indicate that more serious, or at least more permanent, damage has been suffered by their liver.

Post-mortem Evidence of Vascular Defect

The observations recorded by Nolan Lewis (1923) were confirmed. The heart in schizophrenic subjects is small and their main limb vessels are small in calibre. The thinness of the atrial wall is often striking, only a few strands of muscle fibres being visible under the pericardium, although the atria are not dilated. The ventricles are also small, but their musculature is normal, or even slightly hypertrophied. Nolan Lewis is inclined to attribute the aplastic condition of the vascular system of schizophrenic patients to arrested development, but it is possible that it may depend on a circulatory dysfunction, a low blood pressure and possibly a diminished volume of circulating blood, in patients whose body-build and organs are frequently of the leptosome type.

The attempt to summarize and interpret these observations, which have extended over more than four years, is necessarily tentative and incomplete. The necessity of relating each single observation to the physical environment, as well as to the patient's temporary mental state, became more and more evident. When these considerations were kept in mind, the peripheral vascular disturbance of schizophrenic patients was seen to form part of an exaggerated thermal response, which compensated for decreased heat production by diminished heat loss. As there is some evidence that the circulatory disturbance is more widespread than is usually believed, it is possible that this may be one of the aggravating factors in patients who are acutely disturbed. This point is of some importance, as symptomatic treatment may be followed by both physical and mental improvement.

The failure of the schizophrenic to respond to increased environmental demands, such as a fall in external temperature, by an increase in physical activity and by the appropriate endocrine and autonomic adjustments, has been claimed as a proof of his inability to maintain homeostasis. It might, perhaps with more justice, be described as his successful adoption of normal physiological processes to achieve his abnormal ends. His "alarm or adaptation reactions", a term made familiar by Selye's work, may be said to be "in

reverse". He is able to sustain life, while maintaining the maximal detachment from his environment.

There is some evidence that genetic factors may predispose a potential schizophrenic to a catatonic rather than a paranoid reaction, and somatic changes are certainly more common in catatonia, but when our methods of recording physical changes which accompany mental activity have been perfected it is likely that physiological abnormalities will be recognized in patients whose main disability is a disorder of thought. Our present knowledge of the electroencephalographic responses of schizophrenic patients already suggests this possibility.

Although the schizophrenic is unable to renounce voluntarily his faulty physical and mental reactions, there is some evidence that he is often aware of his detachment from reality. He can at almost any stage of his illness be coaxed, bullied or tricked into resuming, for a few moments, a firmer contact with his environment, and he may then express his awareness of these more normal processes of thought and his unwillingness to assume them. The change to greater awareness is more easily induced by physical than by psychological means, and a rise in blood pressure, the inhalation of carbon dioxide and oxygen and many other physical agents, can initiate one of these miniature remissions. It is not known whether the same easy reversal is also possible in so-called organic schizophrenic reactions. Drugs, toxins, cerebral trauma and tumour, even hæmorrhage into the medial nuclei of both thalami, as observed by Professor Sir Hugh Cairns in a case not yet published which he has given me permission to mention, may all give rise to mental syndromes which are difficult to distinguish clinically from schizophrenia. It would obviously be of great interest to ascertain whether in these cases the mental symptoms and the somatic manifestations, if any, can be modified or temporarily relieved by the same measures as are found effective in the so-called "functional" psychosis.

The possibility that a schizophrenic may adopt more normal processes of thought remains almost to the end, but his improvement is usually fleeting, unless he can be diverted from his faulty orientation. The remarkable, and at present still unexplained action of insulin, and in some cases of leucotomy, appears to favour this reorientation at the emotional level.

We still know very little of the relation of physical to mental events and even less of its variation under pathological conditions. It is likely that when this relationship is better understood it may prove to be one of the main causes of the puzzling variability of the somatic manifestations of schizophrenic illness.

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Dr. Denis Hill said that in the United States the work of Gellhorn and of Hoskins had attracted much attention. Gellhorn's outstanding contribution was that he had demonstrated a sluggish reactivity of the sympathetic-adrenaline system to stress in schizophrenics. Gellhorn conceived this as a defect in the hypothalamic autonomic centres. Hoskins' contribution was that he collected a large amount of data demonstrating that for many metabolic functions the average variability in schizophrenics was nearly double that in normal persons of the same age. It seemed that these patients had a defective capacity to hold to the steady state for many functions. This variability was also observable in the data which the speaker and his colleagues had collected using the electroencephalogram. It seemed that the variability of the EEG patterns was greater in schizophrenia than in other clinical groups and much more diverse than any group of controls they had studied. Records varied from the low voltage "choppy", fast, relatively arrhythmic type described first by

P. A. Davis, through the normal alpha types to the predominantly slow, fast and slow dysrhythmic types. In acute catatonic schizophrenics, spike discharges were seen in about a quarter of the cases. This phenomena was, of course, common in epileptic and organic conditions.

Catatonic stupor was from the EEG point of view of exceptional interest. Grey Walter reported in 1941 that phases of stupor coincided with a change in the record to dominant low voltage very slow activity. With D. Rowntree, the speaker had confirmed this on a number of patients but the relationship was by no means a simple one. At times there was no strict coincidence of behaviour with EEG change, the clinical change appearing first. At times the EEG changes became more severe as the patient recovered. Patients with recurrent catatonia had been studied, and it was also found that the frequency change varied from attack to attack. At times this was to a less than 2 c/sec. and at others to a very rhythmical 5 c/sec. activity, nor was there a strict agreement from attack to attack for the cortical areas involved in the changes, the rhythmical 5 c/sec. activity being at times frontal, at others occipital. On the other hand, the irregular less than 2 c/sec. activity was invariably in the central regions. The cause for this irregular very slow activity might be, as Dr. Shattock suggested, a secondary disturbance in circulation, similar to that demonstrated in the limbs. However, the rhythmical bilateral 5 c/sec. activity must suggest an altered function in thalamocortical relationships, and activation of the diffuse non-specific thalamo-cortical system discovered by Dempsey and Morison.

Finally, some of the problems presented by Gellhorn's work had suggested some experiments to the speaker and his colleagues. The results had already been reported at the York Meeting of the R.M.P.A. in 1949, and would not be repeated in detail. The EEG, the electrical resistance of the palmar skin and the ECG had been recorded continuously during the thirty minutes after standard injections of I.V. insulin. Special apparatus was used to detect the first changes in the EEG reflecting the cortical changes to progressive hypoglycæmia. In controls the cortical EEG changes preceded the sympathetic adrenaline discharges seen in the precipitous fall in skin resistance and the rise in heart rate. After this the rise in blood sugar followed. In schizophrenics this order of events was not the rule and the EEG changes and the sympathetic adrenaline responses were late in time and at lower levels of blood sugar than in the controls. In catatonic stupor, no change in the EEG and no sympathetic adrenaline responses occurred at all, despite very low levels of blood sugar. In these cases no homeostatic response to the hypoglycæmic threat could be observed. In schizophrenics as a group these responses were late. In view of the apparent dependence of the sympathetic-adrenaline response upon the preceding EEG change in the cortex, it seemed possible that the primary defect lay in the cortex rather than the diencephalon, as Gellhorn suggested. However, the problem was not a simple one, since the EEG change to theta rhythm was itself known to be dependent upon the activity of subcortical centres.

Dr. J. F. Donovan: Since the operation of leucotomy and allied surgical procedures have been widely used in the treatment of schizophrenia, many neurosurgeons have remarked on the appearance of the schizophrenic brain *in vivo*. At the recent discussion of Anglo-American neurosurgeons and psychiatrists there was unanimity of view among the neurosurgeons that the brain in a large number of schizophrenics presents an abnormal appearance. Professor Pool (1949) stated that in at least 50% of cases on whom he had operated there appeared to be widened sulci, narrow gyri and thickened arachnoid, while the cortex seemed hard and yellow. Puech (1949) estimated this abnormal appearance to exist in as many as 72% of cases.

Unfortunately the use of the term "cortical atrophy" to describe this appearance has led to a conflict of opinion with the neuropathologists who have, for the most part, found no atrophic changes in the brains of schizophrenics either macro- or microscopically.

Before dismissing these observations of the neurosurgeons as without foundation I think that one must examine any other evidence which presents itself. There have been many published references to abnormalities noted in the air encephalograms of schizophrenic patients (Jacobi and Winkler, 1927; Lemke, 1935; and Moore, Nathan *et al.*, 1935) but one of the difficulties encountered in assessing the significance of such findings is due to the lack of knowledge of the possible range of variation of the normal encephalogram or of what changes may occur with age alone. Heinrich (1939) has reported that in a series of 100 encephalograms on normal subjects there were considerable changes in appearance according to the age of the subject, while inequality of the lateral ventricles was common, the left usually being larger than the right. However if one adopts a standard which allows for a considerable degree of latitude in the appearance of the normal encephalogram a study of encephalograms of schizophrenics will still show a number which cannot be passed as within normal limits.

In a series of 31 schizophrenic patients, mostly of the catatonic or hebephrenic type, on whom I have carried out air studies only 5 had encephalograms which might be classed as within the conventional standards of normality, while 15 showed well-marked abnormalities. The remaining 11 cases of this group I have included with the normals as being doubtfully normal. Thus approximately half the patients were considered to have abnormal encephalograms.

These definitely abnormal encephalograms were not confined to patients of the highest age-group in the series. The greatest incidence was in the 41–50 age-group but there were cases occurring in the age-group above and below this one. Only 2 of the 15 cases with marked abnormalities in the encephalogram had previously had any of the physical methods of treatment, while 6 of the remaining 16 cases had been given either convulsive or insulin treatment. It would appear therefore, that in spite of the views expressed by some neurosurgeons, treatment cannot be implicated as a cause of the apparent brain shrinkage.

A number of these cases subsequently had the operation of leucotomy. Of 11 cases where the neurosurgeons had remarked on the abnormal appearance of the brain at operation, there were 7 who had shown marked abnormalities in the air encephalogram. One case with a normal air encephalogram was stated to show atrophy at operation.

It has been suggested that barbiturates or other drugs used for premedication before operation of encephalography may be responsible for the appearance of apparent atrophy of the brain. To investigate this the usual premedication in some patients was omitted and serial X-ray pictures were taken over a period of several hours following the air replacement.



FIG. 1.—M. P., aged 39. Air encephalogram, showing inequality of lateral ventricles, the dilatation being on the right side with collections of air in the parietal region at the vertex.

The administration of drugs such as sodium amytal or omnopon, or in one case 50 c.c. of 50% sucrose given intravenously, had no apparent effect on the appearance of the encephalogram. However in 2 cases it was observed that before any drug was given the ventricles were undergoing a process of dilatation and in one case the dilatation occurred unilaterally.

In searching for other evidence as to the nature of these abnormalities one naturally turns to the EEG findings. Of the present group nearly half have had EEG investigations and the findings have been for the most part non-specific abnormalities of the slow wave or "choppy" type but three I think deserve special mention.

One patient (J. R.), aged 47, has a fairly typical hebephrenic illness commencing at the age of 23. He has been inaccessible for the last ten years. There is no personal or family history of fits, neither has he had any physical illness likely to have any bearing on his mental state. The EEG shows a slowed alpha rhythm of about 7 c.p.s. but with components of 5–6 c.p.s. This type of EEG has not been described as occurring in any but organic cerebral disorders. The air encephalogram shows evidence of diffuse shrinkage of the cortex.

The second patient (E. S.) shows some dilatation of the left ventricle and a collection of air over the left parietal region in her air encephalogram. Her resting EEG record shows little in the way of abnormalities but during photic stimulation a well-marked asymmetry of response is seen. Again asymmetry is seen in the response to injection of sodium amytal

FIG. 2.—EEG of M. P., aged 39. (A) Resting record. (B) Photic stimulation at 4 f.p.s. (C) After 8 c.c. 5% sodium amytal I.V. (D) During amytal-induced sleep.

intravenously, the fast activity so produced being of much greater amplitude in the left frontal region.

The last patient (M. P.) again shows inequality of the lateral ventricles in her air encephalogram, the dilatation being on the right side with collections of air in the parietal region over the vertex (Fig. 1). Her EEG (Fig. 2) shows only asymmetry of the alpha rhythm in the resting record but there is fairly marked asymmetry in the response to photic stimulation and in the production of fast activity by intravenous sodium amytal. In amytal-induced sleep slow waves occur to a greater extent in the left hemisphere.

Conclusion

In these three typical schizophrenics the combination of EEG abnormalities and changes in the air encephalograms appears strongly suggestive of some organic cerebral pathology. With the use of methods of activating the EEG a greater proportion of abnormalities may perhaps be found in schizophrenic subjects.

Whether neurohistology will eventually show any pathological change in schizophrenic brains is a matter of speculation but there would appear to be evidence that cerebral shrinkage does occur in a high percentage of patients. Much further investigation is required before one can say anything about the importance of these findings. Points that should be decided are whether or not the changes are reversible and whether they are an indirect result or a part of the schizophrenic disease process.

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Section of Physical Medicine

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DISCUSSION ON THE SIGNIFICANCE OF CONGENITAL ABNORMALITIES OF THE LUMBOSACRAL REGION

Mr. J. R. Armstrong: The lumbosacral region is one of the danger spots in the spinal column. It is subjected to forces greater than anywhere else in the body and there is acute change in the direction of transmission of these forces at this level. The mechanics have been disorganized by the assumption of the upright position.

Everyone at some time or another in their life has had some degree of low back pain. The causes of low back pain form a large ill-defined group which is only gradually being reduced to order.

Among the possible causes are the developmental anomalies or variations from the normal which are particularly common in this region. Are these anomalies significant? It is true that they are mainly seen in X-rays of people with low back pain but it is mainly people with low back pain who have their low back X-rayed. They are commonly seen in X-rays of people with no low back pain.

Although there are many such anomalies I think it is possible to classify them in five simple groups. In my view they are not, with one exception, often of significance.

GROUP I.—*Failures of posterior fusion.*

Three centres of ossification—one for body and one for each half of neural arch. Failure of posterior fusion produces a spina bifida. This may be a bony defect only or may involve the meninges, the spinal cord or the cauda equina. I would suggest that the bony abnormality is never significant and only assumes importance in association with abnormalities of meninges, cord or cauda.

GROUP II.—*Spondylolysis and spondylolisthesis.*

Occasionally in the fifth lumbar vertebra and very occasionally in the fourth or other vertebra each half of the neural arch is formed from two centres of ossification. One centre is responsible for the ossification of pedicle and upper articular facet, the other for the inferior articular facet and the lamina. The line of cleavage passes between the two articular facets.

Fibrous union may occur without material displacement—spondylolysis.

Separation may occur with forward displacement of the vertebral body in relation to the sacrum, the inferior facet and lamina remaining in the normal position.

Spondylolisthesis is an undoubted cause for symptoms. These may occur early or late and may be mild or severe. They may be associated with root symptoms due to kinking of the roots of the cauda equina either in their extrathecal or intrathecal course. They may be relieved by exercises and corset or may require fusion. They are commonly found in association with a disc lesion at the interspace immediately above or below the spondylolisthesis.

GROUP III.—*Abnormalities in the number of mobile vertebræ in the lumbar region.*

Normally there should be five mobile lumbar vertebræ. Commonly six or four mobile vertebræ may be found. This appearance may be false, due to abnormalities of the lower rib, or true, due to lumbarization of the first sacral vertebra or sacralization of the fifth lumbar vertebra. The presence of four or six vertebræ is not in itself significant although

the spine with six mobile vertebræ may be more subject to postural strains. Partial sacralization of the last free vertebra may produce symptoms. The transverse process may be completely or incompletely fused with the sacrum. If completely fused it is probably not important. If incompletely fused a false joint may be formed and arthritis may occur at this joint, and thus produce symptoms. It should be noted, moreover, that the fourth lumbar root or the fifth lumbar root, depending on the level of the vertebra involved, can be in close anterior contact with such a joint and may be irritated by arthritic change.

GROUP IV.—*Abnormalities of the plane of the articular facets.*

Normally the articular facets of the upper lumbar vertebræ are in the antero-posterior plane and the lumbosacral facets in the lateral plane. Variations, either unilateral or bilateral, in the plane of the facets are very common. Great importance has been attributed to such variations by certain schools of thought. They are said to be associated with arthritic changes and root irritation in the region of the foramina. This line of thought started with Sicard in 1916, was probably best expressed by Putti in his Lady Jones Memorial Lecture in 1927, is still popular on the Continent and has died or is dying very hard in this country. I do not believe that variations in the planes of the facets are an important cause of arthritis or that arthritis when it does occur produces irritation of the roots. Such arthritic changes when seen in association with sciatica are almost invariably secondary to disc lesion at the same level and this disc lesion accounts for the root irritation.

GROUP V.—*Congenital abnormalities in the discs themselves.*

There are small schools of thought both in this country and in America which attribute disc lesions to congenital anomalies of the discs themselves. The supporting evidence for such contentions seems to me insignificant.

Dr. F. Campbell Golding: There are few regions of which less is known as to the clinical significance of radiological findings or the mode of formation of some of its abnormalities than the lumbosacral spine. Many lesions appear to be due to the combination of trauma, degeneration and congenital abnormality.

For example, what importance should be attached to the presence of spina bifida of Sacral 1, to sacralization of Lumbar 5, to a narrowed lumbosacral disc, to a unilateral or bilateral hiatus in the pars interarticularis of a vertebra, to osteitis condensans ilii, to calcification, or to the presence of gas in a disc?

A spina bifida of Sacral 1 is relatively common. In fact it is so common that a radiologist may not consider it worth mentioning in his report, but some surgeons believe that it is directly related to nocturnal enuresis in adolescents and operations are performed on these patients in some clinics. We examined 100 consecutive films of the sacral spine at the Middlesex Hospital. These were all routine examinations and the patients were adults. It was found that 19% had a spina bifida of Sacral 1. A series of cases of nocturnal enuresis in children has been collected by Dr. R. E. Glennie at the Hospital for Sick Children. He found that there was a higher proportion of spina bifida in the controls than in the enuretics in a series of 299 children of which 73 were controls. (This work has not yet been published.)

Secondly, does sacralization of a transitional vertebra cause symptoms? Ten or fifteen years ago this was not doubted. I have seen the statement that 50% of patients with sacralization complained of symptoms. At the present time little notice is often taken of this abnormality. I do not know whether a unilateral sacralization causes symptoms but there are three radiological reasons why it may do so. It can be noted that the unilateral sacralization may form a false joint and the margins of this joint are often sclerosed with local lipping, secondly the patient may develop a local scoliosis and thirdly it is not uncommon to find a local protrusion of the disc—not at the site of sacralization but at the disc above it.

What is the practical value of the radiological evidence of a narrowed lumbosacral disc? Firstly, it is of no value when accompanied by sacralization, as this disc is variable in width, and secondly this is a common congenital anomaly—a fact which may not be appreciated by all observers. To demonstrate this point we obtained lateral films of 100 patients sent for barium enemas. Of these, 44 had relative narrowing of the disc. This is obviously of importance if narrowing of the disc is considered to be the first sign of nuclear protrusion. It is therefore of more practical importance to note a slight relative narrowing of the disc of Lumbar 4–5 than Lumbar 5–Sacral 1.

One sees many examples of escape of the nucleus of the disc into the body. It occurs in adolescents in osteochondritis of the spine and also in a rare condition when the epiphyses are unaffected. The latter gives a typical radiological picture as the nodes are symmetrical and affect many bodies.

In adults this common condition is known as the Schmorl's node. A simple rule in diagnosis is that the narrowing of the disc is proportionate to the amount of nucleus which has been lost, and the latter is clearly visible as it is demarcated by a thin layer of compact bone; if this were not present the node would not be detected by radiology. It should be noted that a fracture which disrupts the disc may cause considerable narrowing, and a body may even be split in half by the nucleus pulposus.

The Schmorl's node may be due to a congenital weakness or to degeneration of the disc plate. The minor traumata of daily life are presumably the ultimate factor. It is worthy of note, however, that many of these nodes form in the body beyond the normal boundary of the nucleus pulposus and this is very difficult to explain satisfactorily.

In adolescents and in some adults one can determine the position of the nucleus because it causes a smooth indentation on vertebral surfaces. This finding is very common in adolescents and is of no significance.

In routine work one occasionally sees a similar impression on the disc surface of a vertebra; it appears to be due to the nucleus, but may be near the anterior margin of a vertebra and it is suggested that the nucleus may move within the substance of the disc. At the present time it is usually considered that the nucleus is either in the normal position or—if it has moved—then it presents in the spinal canal as a protrusion. On radiological evidence it appears possible that anteropulsion, retropulsion or lateral displacement of the nucleus can occur. It is possible, also, that this is the explanation of the presence of Schmorl's nodes in the anterior part of the vertebra, the explanation usually offered for this phenomenon being that loose cartilage cells beneath the disc plate have multiplied.

A peculiar feature of calcified discs is that many patients are middle-aged rather than senile. A few are sent to the X-ray Department complaining of pain in the back, but many cases of calcification of the disc are found accidentally. There does not appear to be any reason why this condition should cause symptoms.

The presence of a gas shadow in some part of the disc is more common than one might believe. The shadows are only visible in the lateral film and are often thought to be due to air in the colon. They occur in any part of the disc. They are not confined to the nucleus. They are said to disappear when the patient is upright and to reappear when he lies down. Their mode of formation—like other vacuum phenomena in joints—is said to be by extraction of gas from body fluids, but discs are relatively solid and avascular. It is, therefore, probably safe to say that they are positive evidence of degeneration of the disc.

One of the commonest subjects for discussion at medical meetings is pain in the lower back. In lordosis, one possible cause (which is doubtless in the literature) is the impact of spinous processes on one another. The opposing surfaces of these appendages become deformed and sclerosed, simulating a false joint. It would seem probable that this causes pain, but I have not seen it mentioned.

Osteitis condensans ilii is a peculiar lesion. The most striking feature is the high incidence in women, particularly multipara, but it is also found in women who have not had children and in men. It is often an incidental finding in X-ray departments but it may also cause pain in the lower part of the back. I examined the notes of 17 patients at the Orthopædic Hospital: of these, 16 were referred to the department for pain in the sacral region. All of these patients were women, the youngest was 20 years and the oldest 58 years; in 5 patients the condition was unilateral. No satisfactory explanation has been offered for the cause of this lesion. This condition resembles the early changes of ankylosing spondylitis and is often confused with this disease, but the two are not related since the spine is never affected in osteitis condensans ilii.

It is possible that the lesion is related to the osteitis of the symphysis pubis which is found after pregnancy and one of these cases suggests this relationship, since the X-ray appearance of the two lesions is almost identical.

In this series there are 80 cases of spondylolisthesis consisting of 56 males and 24 females; these have been collected over a period of ten years. I know two surgeons who set out to discover the cause of spondylolisthesis. Each obtained a large series of cases and applied himself to the problem for a long period, but both confess that they have failed.

There are arguments in favour of the theory that the primary lesion is congenital, and there is the evidence of other congenital defects which are sometimes found with an hiatus in the pars interarticularis, such as spina bifida and defects in the intervertebral facets. A considerable amount of work has been done to try to demonstrate two centres for each side of the neural arch, but with one exception (Batts, 1939) this has failed. The conclusion of these workers is that a double centre which fails to unite is not the cause of the hiatus in the pars interarticularis.

Until a few years ago the traumatic theory was not popular, but recently it has been suggested that the condition is a fatigue or stress fracture.

An examination of oblique films or dried specimens of the spine shows that the pars interarticularis is constant in width throughout the lumbar spine, or becomes progressively wider from Lumbar 1 to Lumbar 5, and as the latter is relatively short, it is therefore comparatively strong. It can also be seen by close examination of routine oblique films that this finding is subject to variation. In some individuals the isthmus varies in width in different regions and it may become progressively narrower from Lumbar 1 to Lumbar 5. It is suggested therefore that the basic fact in causation of spondylolisthesis is a congenital variation in the width of the isthmus and it is the thin isthmus which breaks.

The radiological evidence of oblique films often suggests that the lesion is a fracture; it has not the smooth edges of a congenital anomaly. The fact that callus does not form at the site is understandable since callus does not occur in other vertebral injuries. A fracture of this region, which was discovered immediately and treated, has been reported recently, and the films show that bony union occurred (Roche, 1948). It is known that a vertebra may slide forwards or backwards although there is no break in the pars. The forward displacement is as great as that of a first or even second degree spondylolisthesis and is caused by degeneration of the disc, but it has also been stated that it is due to overriding of the facets. This condition occurs in older patients, in this series all were over 50 years of age and the distribution in the sexes was approximately equal. The direction of displacement is influenced by the normal lumbar lordosis and the displaced body tends to move backwards in the upper and forwards in the lower lumbar spine. This condition is more common at the level of Lumbar 4–5 than at Lumbar 5–Sacral 1. Willis (1935) said that reversed spondylolisthesis was an optical illusion at Lumbar 5–Sacral 1. It is true that it may be an optical illusion at this level and due to faulty X-ray technique, but it also occurs as a fact.

It is probable that abnormal mobility of a vertebra is the most common cause of symptoms in this condition and in the true spondylolisthesis. This suggestion is based on the analogy of the tuberculous joint. The latter may heal with fibrous ankylosis retaining a few degrees of painful movement. In the same way the slight movement of a vertebra may cause pain. This abnormal mobility can be demonstrated by lateral films in the upright position. These are taken in full flexion and full extension. In a proportion of cases and depending upon the efficiency of the manœuvre, the vertebra can be rocked forwards and backwards, but the extent of the movement is slight.

In conclusion, I have tried to show that the importance of radiological findings in this region is very difficult to assess. The only method of uncovering facts is by the examination of large series of patients and by improvement in radiological technique, and in this respect many advances have been made in the last few years.

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Mr. Harvey Jackson: In enquiring as to the significance of these structural abnormalities we have to consider the parts played by the defects as well as the implications in respect of other structures. The associated misalignments of the spinal axes must throw odd stresses and strains on soft structures as on articular surfaces appertaining to the spinal column. Apart from these demonstrable structural defects their very presence suggests that yet other developmental anomalies may exist if not in the spine then in other parts of the skeleton. A spina bifida occulta may be all that is revealed on X-ray but in more extensive defects of the nature of spina bifida due implications of associated deformities must be considered. Indeed it is most important before any operative reconstruction of these defects is undertaken to be assured that the spinal lesion is not just a part of more complex developmental abnormalities affecting the cerebrospinal axis. It is certainly disconcerting for an operation on the spine to be succeeded by a state of progressive hydrocephalus. The relatives of a patient so operated are apt to assume a rather blameworthy attitude towards the surgeon.

The diagnosis of disc protrusion has been established for only fifteen years or thereabouts. Yet it is forty years since Goldthwaite of Boston proposed such a lesion as a possible source of many cases of pain involving the back and the lower limbs. How do we account for such delay? It would appear that the problem of arriving at a true concept is sometimes obscured in the differentiation of cause and effect. The use of the terms "sciatica" and "sciatic scoliosis" by neurologists and orthopædic surgeons has diverted attention towards the lower limb thus veiling the spine as the primary source of the disorder. Another difficulty presented

by the clinical state of certain disc protrusions has arisen from a misunderstanding of particular root phenomena, e.g. the occurrence of depression of the knee-jerks with some disc lesions situate between the fourth and fifth lumbar vertebræ. Herein we must not hold too rigid a definition of the distributions of particular nerve roots. Pre- and post-fixation is to be applied to the lumbosacral plexus as with the brachial plexus. Indeed it is my personal opinion that three quite different outlines of the surface distribution of the fifth lumbar root can be delineated in accordance with the conformation of the spine in terms of normality lumbarization or sacralization.

The presence of Schmorl's nodes not uncommonly is met by radiological reports of nuclear herniation into the vertebral bodies. One wonders what is the true status of these formations, certainly there is little proof available that herniation is their true mode of formation. It is my opinion that such regular shadows imply incomplete development and their very existence indicates the feasibility of the presence of yet other structural abnormalities. Furthermore, it would appear that the presence of one form of structural defect in the spine is supportive evidence of a diagnosis of disc protrusion where evidence of a focal lesion is clinically recognizable. A high proportion of radiographs of the lumbosacral spine of patients proved at operation to be victims of disc protrusion show one structural defect or another, e.g. spina bifida, articulated transverse processes, lumbar ribs, Schmorl's nodes, &c. That Schmorl's nodes in themselves ever give rise to any clinical disturbance is not appreciated.

Reference has been made to collapse of intervertebral spaces as confirmation of the presence of disc protrusions. It seems to me that such disclosures are dubious forms of corroboration. So often does one see reduction of the space between the fifth lumbar vertebra and the first piece of the sacrum that unless the clinical picture envisages a protrusion at that particular level the radiographic appearances should be discounted. When the clinical diagnosis is determinable with some degree of certainty it is not uncommon to see a wedging of the affected disc, the wider side of the wedge appearing on the side of the lesion.

When the causation of disc protrusion is under consideration trauma is generally held to be an important factor. That trauma is a precipitating factor in an attack of lumbosciatic pain is without doubt but the intensity of the trauma is usually almost insignificant, e.g. bending to tie a shoe-lace, reaching to take something from an elevated shelf. How such a limited force could bring about enough distortion of the spine to extrude intervertebral disc tissue is difficult to appreciate. Moreover not infrequently one meets with a case of a typical "Disc" the first notification of which occurs when the patient is restricted to bed with an influenzal attack or other acute febrile illness. Again the symptomatic development during pregnancy is undoubted. What is the mechanism of action of these several quite different precipitating factors? Surely we must consider the possibility of a pre-existing lesion that undergoes some precipitating change arising out of trauma, toxæmia or endocrine effects. Could it not be that a disc protrusion is a structural defect of developmental origin? The demonstration radiologically of associated structural defects of the lumbosacral spine or of the general skeleton would then afford proof of the state of structural abnormality in the particular patient and support a suspicion of other lesions of like origin.

Dr. Campbell Golding has referred to rarefied areas in the discs due to the presence of gas. One wonders if these are not the outcome of cavitation within the discs? Throughout life there appears to be some tendency for cavitation to take place for one reason or another. It would appear that several processes are responsible, varying with the different decades of life, hence cavitation is prone to increase with advancing age.

Dr. H. W. Gillespie: An accurate assessment of the frequency and significance of lumbosacral abnormalities depends on figures obtained from large-scale investigations. Brailsford (1929) examined 3,000 spines and found 26·4% developmental irregularities but from his selection of cases, one is not justified in regarding this as the normal incidence of congenital abnormalities in the lumbosacral spine. Gillespie (1949) examined, at St. Peter's Hospital, Botleys Park, the lumbosacral spines in a series of 500 laminectomies for disc protrusion and compared them with a series of 500 normal spines. The disc lesion series revealed 34·2% lumbosacral abnormalities, either in the form of a transitional lumbosacral vertebra, alteration in the number of lumbar vertebræ, or spina bifida, whilst only 8·8% of irregularities were found in the normal series. The discrepancy between these two figures has a bearing on the significance of congenital abnormalities. The last few years have produced a change in our outlook on the causation of backache, largely through the realization of the importance of disc lesions. In the light of these advances, the presence of congenital malformations in the lumbosacral spine assumes a new role. Although congenital malformations themselves are not the cause of backache, they appear to predispose to disc

protrusions. Recent work on discs suggests that there may also be a relationship with a congenitally abnormal nucleus pulposus. It would therefore be wrong to isolate lumbosacral bone irregularities from concomitant abnormalities in the soft-tissue structures. The osseous defect, however, is most readily demonstrated in the radiograph.

REFERENCES

BRAILSFORD, J. F. (1929) Deformities of the lumbosacral region of the spine, *Brit. J. Surg.*, **16,** 562.
GILLESPIE, H. W. (1949) The significance of congenital lumbosacral abnormalities, *Brit. J. Radiol.*, **22,** 270.

Dr. B. Freedman: Congenital absence of part or whole of the sacrum and coccyx is rarer by far than any of the abnormalities to which reference has already been made, only 45 cases having been reported (Freedman, 1950). The condition is one of great interest from the embryological point of view. It is associated with agenesis or hypoplasia of the corresponding spinal nerve roots and of the muscles supplied by them. There is consequently marked wasting or absence of the muscles of the buttocks and legs (L.5–S.1), and perineum (S. 2–5). Clubfoot, urinary incontinence, or abnormalities of the viscera are commonly present. The last are almost all confined to the genito-urinary system or rectum. Walking is usually possible. The condition may be commoner than the number of recorded cases suggests, and I would urge that the sacrococcygeal region be X-rayed in all cases of congenital deformity of the lower limbs, of the genito-urinary system or ano-rectal region.

[X-rays were shown of a case in which there was absence of the vertebral column below the level of the second sacral segment.]

REFERENCE

FREEDMAN, B. (1950) *Brit. J. Surg.*, **37,** 299.

Dr. E. J. Crisp: It should be obvious that congenital abnormalities in the lumbosacral region diminish the factor of safety and thus predispose to disc lesions.

Normally, the fifth lumbar vertebra nestles snugly on the sacrum between the iliac crests, stabilized laterally by the powerful iliolumbar ligaments, and protected posteriorly by the strong lumbosacral interspinous ligament.

Thus, spina bifida occulta of the first sacral segment, especially when the spinous process is rudimentary and unattached to either lamina, deprives the lumbosacral disc of one of its main protective components. Likewise, when the fifth lumbar vertebra is sacralized (i.e. fused to the sacrum) so that there are only four lumbar vertebræ and the L.4–5 joint becomes in effect the lumbosacral joint, the lowest mobile lumbar vertebra is perched above the iliac crests and accordingly deprived of the important stabilizing effect of the iliolumbar ligaments. It is easy to see that this arrangement must render the lumbosacral joint vulnerable to strain. Though a sacralized fifth lumbar transverse process may cause pain on the side of the sacralization, it more often leads to a contralateral lumbosacral disc lesion. The false joint between the abnormally large transverse process and the sacrum appears to interfere with the normal mechanism of rotation at the lumbosacral joint, and acting very much as a hinge causes undue torsion to the disc on the contralateral side.

In similar manner abnormalities in the arrangements of the apophyseal joints, whereby one is in the anterolateral and the other in the transverse plane, must contribute to disc lesions by limiting movements in certain directions in the affected intervertebral joint, and thus interfering with the mechanical efficiency of the lumbar spine as a whole.

Spondylolisthesis it is self-evident must subject the affected disc to very considerable distortion with its consequent effects.

Dr. Kenneth Lloyd showed the X-rays of a man aged 48, a traffic inspector, who had been complaining for the past nine months of pain of L.1 distribution on the left side which was worse after standing at his work and eased by rest. There was no history of trauma.

The X-rays showed a loss of continuity of the pars interarticularis of the first lumbar vertebra on the left and a similar loss of bony continuity across the right inferior facet articulation of L.2. It was thought that these appearances were not due to fractures, but a failure of union of abnormal centres of ossification.

It was suggested that this man was a future candidate of spondylolisthesis, of which there was no evidence at present, and that these findings were supportive evidence of the congenital origin of this deformity.

[*May* 10, 1950]

SAMUEL HYDE MEMORIAL LECTURE

NUMBER 9

Medical Applications of Microwave Diathermy: Laboratory and Clinical Studies [1]

By FRANK H. KRUSEN, M.D., F.A.C.P.

Professor of Physical Medicine, Mayo Foundation. Head of Section on Physical Medicine, Mayo Clinic, Rochester, Minnesota, U.S.A.

IT is a great honour to have the privilege of delivering the Samuel Hyde Memorial Lecture and to follow, in honouring the memory of Samuel Hyde, such distinguished physicians as R. Fortescue Fox, William Gordon, H. Whitbridge Davies, Sir Henry Cohen and Philip S. Hench. Dr. Hyde was born at Stalybridge 101 years ago, was privately educated and afterwards entered King's College, London, in 1872. In 1875 he received the certificate of honour in obstetric medicine and in 1877 qualified as a member of the Royal College of Surgeons of England. As a student, he took an active part in mission work and was attached to St. Giles's Medical Mission. He was to retain the missionary spirit throughout his life. In 1877 he settled at Buxton and devoted the rest of his all-too-short life to pioneering efforts for the advancement of that branch of physical medicine known as "balneology and climatology". He became editor of the *Journal of British and Foreign Health Resorts*, he founded the British Balneological and Climatological Society, which was incorporated with the Royal Society of Medicine in 1900, and later was merged with this Section of Physical Medicine. He was also editor of the *Journal of the Balneological and Climatological Society*. Dr. Samuel Hyde died in 1900 after a prolonged illness and was buried in Burbage in his fiftieth year. As S. W. Foss has written: "There are pioneer souls that blaze their paths where highways never ran, . . ."

Hyde was truly such a man, whose missionary zeal aided tremendously in the early development of one of the most important branches of physical medicine.

Sound development of the relatively new specialty of physical medicine will depend on parallel expansion of practice, teaching and research. Research concerning the medical applications of physical agents should start in the laboratory. This should be followed by clinical research. Then, and then only, therapeutic applications should be begun and carried on with continuing controlled research until such time as the clinical uses of the agent in question are well established. The studies I am about to describe have been conducted with such chronologic sequence in mind.

DEVELOPMENT OF THE VARIOUS TYPES OF DIATHERMY

For many years electrical currents or radiations of very high frequency have played important roles in medicine and surgery for heating of tissues. Starting with the work of D'Arsonval who demonstrated in 1890 that high-frequency electrical currents of 10,000 cycles per second produce no muscular contraction but only heating when they are passed through the human body, physicians have been employing increasingly higher frequencies for heating of living tissues. By 1900, high-frequency currents of 1,000,000 to 3,000,000 cycles per second (long-wave diathermy) were in use, and by 1935 electrical currents of still higher frequency, 10,000,000 cycles per second at a wavelength of 30 metres (short-wave diathermy), were being employed [1]. Soon thereafter, application was being made of radiations at frequencies of 100,000,000 cycles per second and at a wavelength of 3 metres (ultra-short-wave diathermy) and writers were beginning to run out of diminutives.

[1]Studies done in conjunction with Dr. Julia F. Herrick, Division of Experimental Medicine, Mayo Foundation; Dr. Khalil G. Wakim, Section on Physiology, Mayo Clinic, and Dr. Gordon M. Martin, Section on Physical Medicine, Mayo Clinic; with the aid of the following Fellows of the Mayo Foundation: Dr. Ursula M. Leden, Fellow in Physical Medicine; Dr. Ralph E. Worden, Fellow in Physical Medicine; Dr. Jerome W. Gersten, Fellow in Physical Medicine; Dr. James W. Rae, Jr., Fellow in Physical Medicine; Dr. Joseph P. Engel, Fellow in Physical Medicine; Dr. Louis Daily, Jr., Fellow in Ophthalmology, and Dr. R. Quentin Royer, Fellow in Dental Surgery.

The Development of Microwave Diathermy

Now I am reporting on the use in medicine of radiations at a frequency of 3,000,000,000 cycles (3,000 megacycles) per second and at a wavelength of 10 cm. This procedure has been called "microwave diathermy". The word "microwave" is a popular term designating a certain range of waves in the radio-frequency spectrum. This range includes frequencies from approximately 1,000 megacycles per second to 30,000 megacycles per second or higher. When expressed in wavelengths, this region of the spectrum is from 30 cm. to 1 cm.

Microwaves can be produced by means of specially constructed tubes such as the magnetron and the klystron. The magnetron was invented by Albert W. Hull of General Electric Research Laboratories in 1920 and the klystron was developed by D. L. Webster of Stanford University in 1938.

Now, the scribes who set down the "Book of Genesis" could report everything in the third person, because they were not participants in the work being reported. Your lecturer is not so deluded as to consider in the same category the work reported there and that which is to be reported here. That is not the point. What I am thinking of is that the old scribes, being outsiders so to speak, were spared the use of the objectionable first personal pronoun which, for the sake of the reader who has not access to certain correspondence, I must use in recounting the genesis of the work on microwave diathermy. This pronoun will disappear after a few paragraphs.

In 1937 I became interested in microwaves. In that year Williams [2] reported that electromagnetic radiations with wavelengths of a few centimetres could be focused, and Southworth [3] pointed out that such radiation could be directed along tubes. These observations led Hemingway and Stenstrom [4] to conclude that these properties, which would permit the direction of a beam to a desired region, might make such radiation particularly valuable in medicine. At that time I [5] agreed with Hemingway and Stenstrom that we should study the medical application of radiations having wavelengths of less than a metre.

In 1937 also, I entered into correspondence with Lee De Forest, the inventor of the triode valve, concerning electromagnetic radiations of a wavelength of 3 cm. I told him that if such radiation could be obtained in sufficient intensity, "it would seem that the therapeutic possibilities might be great". In 1938 I advised F. D. Jewett of the Bell Telephone Laboratories, who was developing the magnetron tube, that "if it ever becomes possible to increase the wattage of such tubes, they should prove suitable for therapeutic purposes". He informed me that a power of only 2 or 3 watts could be generated by the tubes then available and I replied that "for therapeutic purposes it is necessary to have considerably higher wattage".

By July 1938 Dr. Albert W. Hull advised me: "I can promise you at least a hundred watts at any wavelength down to 20 centimetres." In March 1939 I learned of the development of the klystron tube at Stanford University and D. L. Webster of the Department of Physics wrote to me: "I am convinced that therapy is one of the important lines to which we must start applying the klystron very soon." I was also advised that "between 10 and 40 centimetres the klystron has outputs of several hundred watts". It seemed that at last a tube of large enough wattage to provide radiation of sufficient power for medical use had been found.

The idea of using radiations of a wavelength of a few centimetres in treatment was, of course, not an original one. At about the same time (1938 and 1939) that I was investigating the possibilities, Hollmann [6, 7] was discussing the possible application of radiations of a wavelength of 25 cm. for treatment and predicted that these waves could be focused so as to cause heating of the deep tissues without excessive heating of the skin. However, at that time, equipment which could generate such high-frequency waves at sufficient wattage for suitable biologic investigation was not available to Hollmann.

Just when I had finally found tubes that gave promise of being of sufficient wattage, suddenly all such tubes became mysteriously unavailable and it was not until the secret of radar was finally revealed that it became evident that the supply of such tubes had been designated for military use and that the tubes were being employed only for this secret wartime development. As soon as the war was over, I found in January 1946 just what I had been looking for. On a visit to the Massachusetts Institute of Technology, I saw a large experimental model of a microwave generator which contained a water-cooled multi-cavity magnetron with a maximal output of 400 watts and a frequency of 3,000 megacycles per second. Shortly thereafter, in June 1946, I obtained one of these devices[1] and, with the aid of Drs. Herrick, Wakim and Martin, began our studies on microwave diathermy. We

[1]We are indebted to the Raytheon Manufacturing Company of Waltham, Massachusetts, for providing the early models of the microwave apparatus employed in our studies.

also obtained a small, portable experimental model (Fig. 1) of a microwave generator, containing an air-cooled multicavity magnetron with a maximal output of 125 watts, which operated either on a frequency of 3,000 megacycles per second or a frequency of 2,450 megacycles per second, depending on the magnetron employed.



FIG. 1.—Small portable experimental model of microwave generator containing an air-cooled multicavity magnetron with maximal output of 125 watts at a frequency of 3,000 megacycles per second. (Weight 34 pounds [15·4 kg.], dimensions 15 by 10½ by 9¼ in. [38 by 27 by 23 cm.]) Two hemispherical directors of different sizes are shown.

FIG. 2 (Inset to FIG. 1).—The three types of microwave directors which were employed in these studies. (*a*) The director of type A is a hemispheric type 4 in. (10·16 cm.) diameter; (*b*) the director of type B is a hemispheric type, 6 in. (15·24 cm.) in diameter; (*c*) the director of type C is a rectangular or "corner reflector" type.

The multicavity air-cooled magnetron tube was developed through the genius of a research group at the University of Birmingham and was of tremendous importance in perfecting radar which, it has been said, "won the Battle of Britain". Prior to 1940, suitable generators of microwaves for radar did not exist. In September 1940, a British technical mission headed by Sir Henry Tizard brought the multicavity magnetron tube to the United States and in a short time American manufacturers had produced this multicavity magnetron tube for use in microwave radar. The output of these tubes could be as high as 1,000,000 watts and the microwaves which they develop have optical properties so that they can be reflected, refracted or diffracted. They can be focused by a suitable type of metal lens to as sharp a beam as a searchlight. Microwaves can be selectively absorbed by certain media but whether or not the various biologic media will absorb microwaves selectively has not as yet been determined.

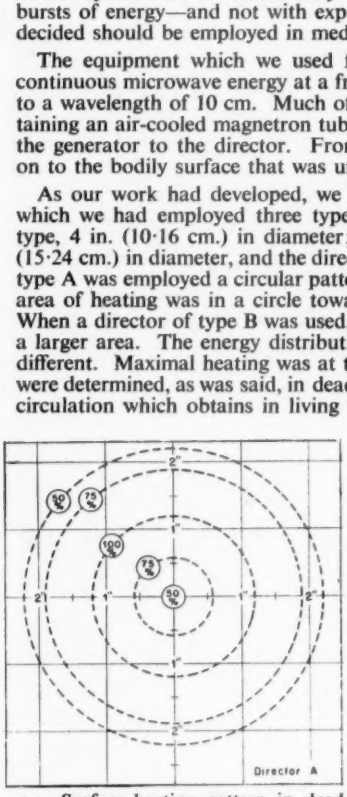
FIRST STUDIES ON THE MEDICAL APPLICATIONS OF MICROWAVE DIATHERMY

Dr. Julia F. Herrick, after years of experience with the Signal Corps of the United States Army in studies of radar, began our work with experimental studies, *in vitro*, on microwave diathermy. Then Dr. Ursula Leden, Dr. Herrick, Dr. Khalil G. Wakim and I [8] began studies on living animals. These studies continued, and I wish to say that most of the actual work was done by my associates rather than by me.

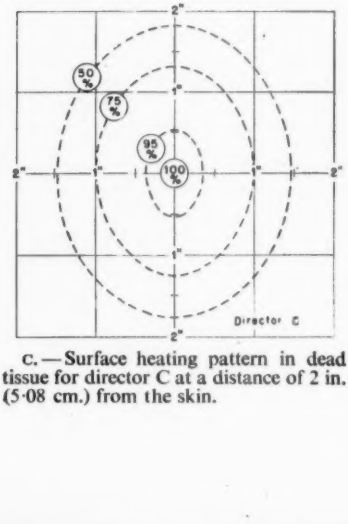
Up to the time when this work began, the only reports of the effect of microwaves on the living organism were of several studies [9–11] conducted by members of the armed forces of the United States in order to answer a problem of morale. They were meant to dispel fears of possible ill-effects of exposure to radar on personnel connected with radar work. These reports were concerned only with exposure to radar pulses—that is, very brief, rapid bursts of energy—and not with exposure to continuous microwave energy such as we had decided should be employed in medicine.

The equipment which we used for our first experiments on living animals produced continuous microwave energy at a frequency of 3,000 megacycles per second, corresponding to a wavelength of 10 cm. Much of our work was done with the small, portable unit containing an air-cooled magnetron tube. The energy was transported by a coaxial cable from the generator to the director. From this hemispherical director, the energy was radiated on to the bodily surface that was under treatment.

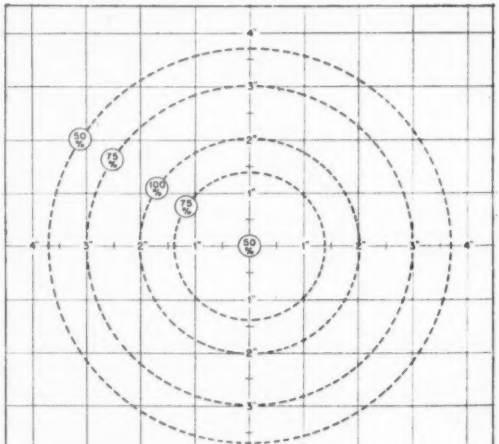
As our work had developed, we had used dead tissue for investigation of directors, of which we had employed three types (Fig. 2): the director of type A was a hemispheric type, 4 in. (10·16 cm.) in diameter; the director of type B was a hemispheric type, 6 in. (15·24 cm.) in diameter, and the director of type C was a corner reflector. When a director of type A was employed a circular pattern (Fig. 3A) was produced, in which the peak, or 100%, area of heating was in a circle toward the periphery and not at the centre of the pattern. When a director of type B was used, the same pattern (Fig. 3B) was obtained but it covered a larger area. The energy distribution pattern for a director of type C (Fig. 3C) was very different. Maximal heating was at the centre of an elliptical pattern. All of these patterns were determined, as was said, in dead tissue and do not indicate the equalizing effect of the circulation which obtains in living tissue.



A.—Surface heating pattern in dead tissue for director A at a distance of 1 in. (2·54 cm.) from the skin.



C.—Surface heating pattern in dead tissue for director C at a distance of 2 in. (5·08 cm.) from the skin.



B.—Surface heating pattern in dead tissue for director B at a distance of 2 in. (5·08 cm.) from the skin.

FIG. 3.

For our early studies on living tissue, only a director of type A was employed. We confined our studies to the area where heating was nearly maximal, as determined by the heating pattern. Trained dogs without anæsthesia were employed in the majority of the painless experiments. When surgical procedures were necessary, anæsthesia was produced by pentobarbital sodium. After considerable preliminary experimentation, it was finally determined that an output of 75 milliamperes, corresponding to 65 watts, and a spacing of 5 cm. from director to bodily surface for a period of twenty minutes were both effective and safe. Our observations in this regard were later confirmed by Salisbury, Clark and Hines [12] who concluded that "the area of cross section of a typical 10 centimetre wave guide is about 28 sq. centimetres. Accordingly one must have a total power of about 90 watts to reach the danger level".

Measurement of local temperature of tissues was accomplished by inserting needle thermocouples into the subcutaneous tissue and muscle at various depths and cutaneous temperatures were taken with contact thermocouples. The thermocouples were removed during the actual application of the high-frequency radiation. The exact spots where the needle thermocouples were to be inserted were marked and the needles were inserted to the desired depths that were marked on the shafts. The first readings following application of radiation were taken one minute after discontinuation of the heating. Temperatures of muscle were recorded at two depths (1·9 cm. and 3 cm.). We were soon convinced that microwaves could heat tissues satisfactorily.

With the technique which we employed, there was a rise in cutaneous temperature of approximately 3° to 5° C. and approximately the same rises occurred in subcutaneous tissue and muscle to a depth of 3 cm. (Fig. 4). However, the increase in cutaneous and

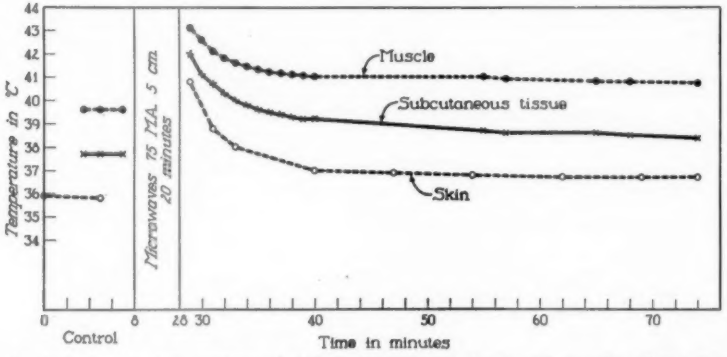


FIG. 4.—Increases in temperature of skin, subcutaneous tissue and muscle, after exposure to microwaves, of the thigh of an anæsthetized animal on which a surgical procedure had been performed.

subcutaneous temperatures was somewhat greater than the increase in temperature of muscle. Superficial muscle, it may be said, rose in temperature more than deep muscle and also cooled more rapidly.

Approximately the same results were obtained when the director was placed at a distance of 5 cm. from the surface and exposure was of 75 milliamperes or 65 watts, as when the director was placed at a distance of 2 cm. from the surface and exposure was of 45 milliamperes or 32·5 watts. In all cases under both conditions, superficial tissues cooled more rapidly than deeper tissues. In intact animals, cooling was always complete and rapid; temperature returned to control value within twenty-five to thirty minutes. In anæsthetized animals on which surgical procedures were performed, cooling was slower and temperature usually did not return to control values but formed a new base line 1° C. or more above the original control value.

For measurement of flow of blood a modification of the Dumke and Schmidt [13] bubble flow meter was employed. It consists of a coil of glass tubing which is introduced between the ends of a sectioned blood vessel. A bubble is introduced by means of a syringe; this bubble is pushed through the meter by the flow of blood and is then caught in the trap to prevent air embolism. The volume of the meter is calibrated, so that by measuring the time necessary for the bubble to flow from marker to marker, the rate of flow of blood can be calculated.

Animals were anæsthetized and heparinized and the meter was placed in the femoral vein. Changes in flow of blood caused by heating of the thigh were observed before, during and after exposure to microwave diathermy. In nine successful experiments, flow of blood after exposure to microwaves increased an average of 109%. Significant increase in blood flow (Fig. 5) usually occurred toward the end of the exposure to microwaves.

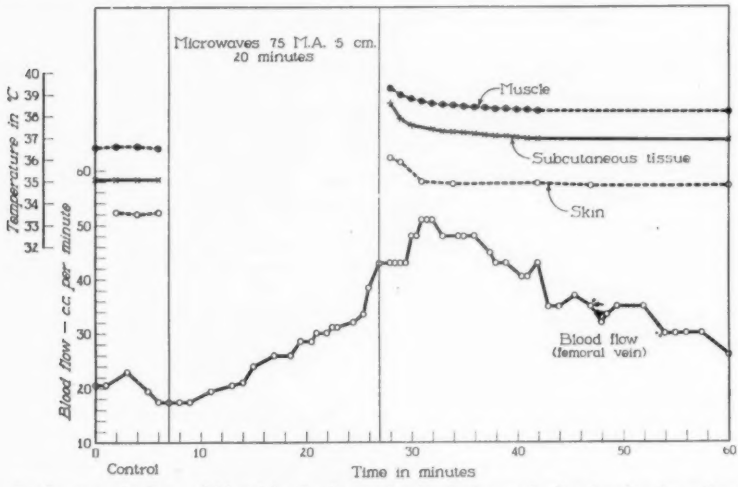


FIG. 5.—Increase in flow of blood in the femoral vein during and after heating by microwaves, of the thigh of an anæsthetized animal; also, increase in temperature of skin, subcutaneous tissue and muscle after the exposure.

The heat produced locally in the tissues by exposure to microwaves causes an increase of venous return and vasodilatation effected through local reflex mechanisms and direct metabolic effects. At this point in our studies, we concluded that microwave diathermy provided a means of heating tissues by which we could obtain accurate localization by direction of a beam of energy toward any surface of the body. We concluded, also, that absorption of such radio-energy was greater than that at longer wavelengths.

At the frequency which we were using, "the absorption of radio-energy in water at 100° F. is in the order of 7,000 times the absorption at 27 megacycles now commonly used for short-wave diathermy" [8]. With better absorption, more efficient heating can be expected. Although we recognized the dangers of excessive dosage of microwaves, we concluded that, with proper technique, they could be employed effectively for heating of living tissues. The wide variety of patterns, and the possibility of placing the director in any position, provided great flexibility in therapeutic application. Freedom from encumbering pads, cables or towelling, commonly used with short-wave diathermy, was possible; moreover, the fact that the radiation could be beamed and localized in the manner of a spotlight facilitated application. Finally, these studies indicated a desirable relationship between cutaneous and internal temperatures which would permit adequate internal heating up to a depth of 3 cm. without undue heating of the cutaneous surface.

Studies of the Effect of Microwave Diathermy on Ischæmic Tissues

About this time, the American Federal Communications Commission assigned the frequency of 2,450 megacycles per second (a wavelength of about 12 cm.) for use in physical medicine. Since this particular wavelength was close to the one we already had been studying, we continued our studies at the assigned wavelength. Dr. Ralph E. Worden, Fellow in Physical Medicine of the Mayo Foundation, continued the studies under our supervision. He attempted to determine the effect of microwaves on the temperature of tissue of which the blood supply was normal, as compared with their effect on the temperature of ischæmic tissue. Also, he sought to determine, if possible, an optimal period of radiation for heating of tissue [14].

A hemispherical director of type A was employed in these experiments and dogs weighing 12 kg. or more were used exclusively. When the effects on tissues with reduced blood supply were studied, the dogs were anæsthetized with pentobarbital sodium given intravenously and, through an abdominal incision, an adjustable clamp was inserted around the aorta distal to the origin of the mesenteric artery. The incision was closed but the handle of the clamp, con-

taining the adjustment screw, was left extending outside the abdomen. Thus it was possible to produce ischæmia of the tissues by clamping the aorta before exposure to microwaves.

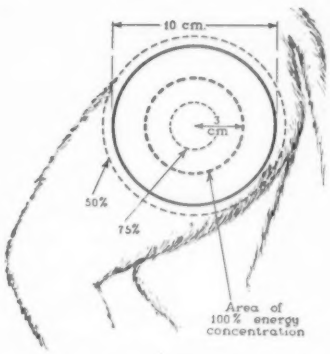


FIG. 6.—The approximate site of exposure to microwaves and the heating pattern produced by a hemispheric director of type A at a distance of 2·5 cm. from the skin.

Cutaneous temperatures were recorded by means of a thermistor [15, 16] (a thermally sensitive resister with a negative temperature coefficient). Temperatures of subcutaneous tissue and muscle were recorded with needle thermocouples. All observations of temperature were continuously registered galvanometrically on moving photographic film. The hair over the thigh of the dog was clipped and an outline of the heating pattern was drawn on the thigh with gentian violet (Fig. 6). The area of 100% concentration of energy, as previously patterned, was outlined and in that area the temperatures of the skin, subcutaneous tissue and superficial and deep muscle were recorded before and after exposure to microwaves. Temperature of muscle was measured at a depth of 1·5 and 3 cm. In all these studies, the output of the generator was maintained at 30 watts and the distance of the director from the skin was 2·5 cm. The aortic clamp was tightened when ischæmia was desired. After a control period, thermistor and thermocouples were removed and the region was exposed to microwaves. Then the thermistor and thermocouples were replaced and the temperatures were recorded, beginning within thirty seconds after irradiation had been discontinued.

During the first five or ten minutes of exposure, temperature of ischæmic tissues did not differ appreciably from the temperature of tissues with intact circulation (Fig. 7). There

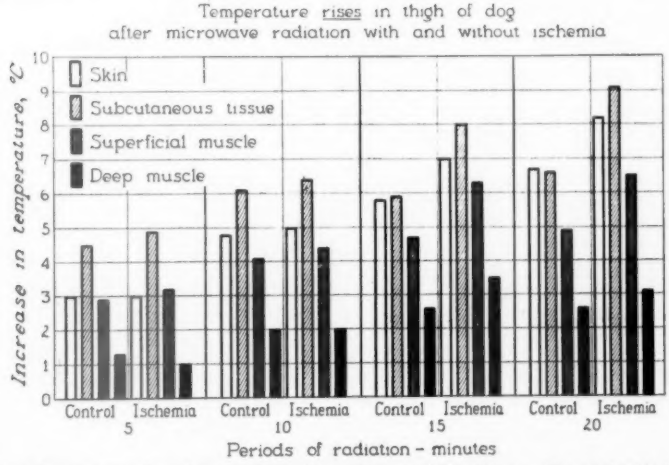


FIG. 7.—Experiments were based on exposure for various periods of time. The control is the average increase of temperature after exposure when the circulation was intact.

was no evidence of burning. However, after exposures of fifteen or twenty minutes, the temperature of ischæmic tissues rose slightly higher than that of tissues with intact circulation. Moreover, in the presence of ischæmia 4 of the 5 animals exposed for fifteen minutes were burned, as were all 6 of those exposed for twenty minutes. In no instance did burning occur when the circulation was intact. Furthermore, in no instance did burning occur when the circulation was intact and irradiation of the same animal at the same site was repeated for six consecutive periods of twenty minutes each.

The highest temperature obtained when the circulation was intact was 44·6° C. and there was no evidence of burning. After ischæmic tissues had been exposed to microwaves for twenty minutes, the highest temperature was only 42·3° C., yet there was gross evidence of burning. The height of the temperature alone is not an indicator as to whether or not tissues will be burned. Duration of exposure and the presence or absence of the protective

mechanism for dissipation of heat provided by the circulating blood are also factors.

In all cases in which burns occurred, the first evidence of burning appeared over the femur where it crossed the zone of 100% concentration of energy in the irradiation pattern of the director (Fig. 8). The greater the prominence of the femur the more severe was the burn. Apparently there is reflection from the bone, with concentration of heat in the overlying tissues. Therefore, microwave diathermy should be employed with caution in areas where there are bony prominences.

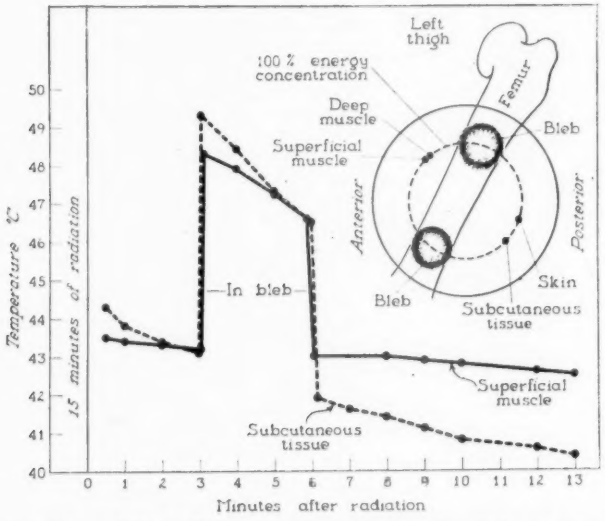


FIG. 8.—Temperature variations after microwave irradiation when blebs are present. The right upper corner shows the relationship of the heating pattern to the femur. In all cases in which burning occurred, the first evidence of burning was over the femur and at a site in which it crossed the area of 100% concentration of energy.

Blisters occurred where the femur crossed the area of greatest intensity of radiation, when the aorta was clamped and the tissues ischæmic. After the aorta had been released and the temperatures had returned to control levels, the same area again was exposed to microwaves for fifteen minutes and temperatures again were recorded at the original sites. It was known that fluids are heated to high levels by microwaves; therefore, after three minutes the needles were quickly withdrawn from the subcutaneous tissue and superficial muscle and inserted into a bleb. The temperature in the bleb was much higher than that of the surrounding tissues. After three more minutes, the needles were removed from the bleb and replaced in their original positions, whereupon the usual cooling curve was resumed. This gave evidence of the high absorption of microwaves in regions of localized accumulation of tissue fluids, and suggested that regions containing fluid such as œdema fluid, regions of effusion, abscesses, the eye, the gall-bladder or the urinary bladder, might be overheated by microwaves unless the dosage was carefully modified. However, it is suggested that, in proper dosage and when indicated, microwaves will be extremely effective in heating such regions.

Another interesting physiologic phenomenon was observed (Fig. 9). The cooling of muscle when circulation was intact was moderately rapid and resulted in a smooth curve, while the rate of cooling of ischæmic muscle was slow, even though it had been heated to a higher temperature to begin with. On release of the aorta, however, cooling of the previously ischæmic muscle occurred rapidly and within two minutes the rate of cooling followed that of normal tissues.

The skin and subcutaneous tissues, with circulation intact, were heated very rapidly and reached high values after five or ten minutes of exposure. The temperature of superficial and deep muscle rose more slowly and all four layers reached a peak in twenty minutes. It was interesting to note that, after thirty minutes of exposure, all of the temperatures dropped below the peak achieved at twenty minutes. It appears that factors which favour cooling become more effective after twenty minutes of exposure. Increasing circulation, as shown previously, is largely responsible for this cooling effect.

Temperature gradients at various levels may vary rather markedly at different periods of exposure. In some instances the muscle layers were the hottest and in others the subcutaneous layer was the hottest. Further studies may reveal that by varying not only the duration of exposure but the output of the generator, and the distance of the director from the skin, different gradients may be obtained.

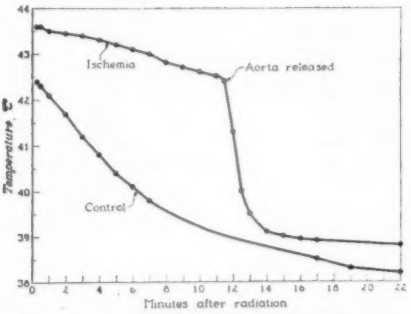


FIG. 9.—Comparison of cooling curves, with and without ischæmia, in deep muscle after fifteen minutes of irradiation with microwaves. The rate of cooling of ischæmic tissue was slower than that of normal tissue even though the rise in temperature was greater. Releasing the aorta resulted in rapid cooling of ischæmic tissues.

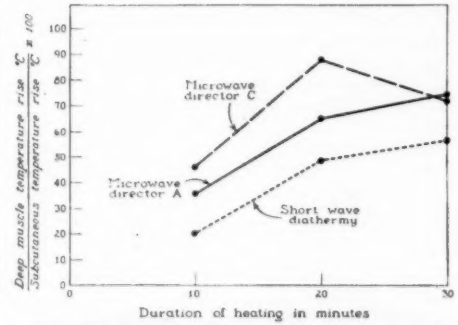


FIG. 10.—Relationship between the increase in the temperature of deep muscles and that of subcutaneous tissues after ten, twenty and thirty minutes of heating. Values shown represent ratio of rise in deep muscles to rise in subcutaneous tissues × 100. All increases in temperature of deep muscles were less than in those in subcutaneous tissue. A value of 100 would indicate a rise equal to that in subcutaneous tissue.

COMPARISON OF THE HEATING EFFECTS OF SHORT-WAVE AND MICROWAVE DIATHERMY

Dr. James W. Rae, Jr., another Fellow in Physical Medicine, contributed a supervised comparative study of the temperatures produced by microwave and short-wave diathermy [17]. A portable microwave generator supplying continuous microwave energy at a frequency of 2,450 megacycles per second and at a wavelength of about 12 cm. was employed for these experiments. Four short-wave diathermy machines, all products of reputable firms and in wide clinical use, were tested. The wavelengths of these four machines varied from 6 to 25 m. Three needle thermocouples were inserted into the tissue, one into the subcutaneous layer, one into the muscle at a depth of 1·5 cm. and one into the muscle at a depth of 3 cm. Cutaneous temperatures were recorded with a thermistor. Temperatures were then recorded on moving photographic film. Four intact and well-trained dogs were used in this study. Basal conditions were approached by permitting the dog to lie quietly on the table for thirty minutes or longer before measurements were taken. The thigh was chosen as the site of application and was kept free of hair by frequent clipping.

One hundred and forty-four experiments were performed with the four short-wave diathermy machines and two microwave directors (types A and C). Twenty-four experiments were carried out with each type of apparatus. These twenty-four experiments consisted of six experiments on each of 4 dogs, and the six experiments consisted of two at each of three periods of radiation; that is, ten, twenty and thirty minutes. The averages of the studies on the heating effect of short-wave diathermy indicate that, before treatment, the temperature gradient in the various layers increases from without inward, the skin being the coolest and the deep muscle the warmest. With short-wave diathermy, the temperature of all four layers increases after ten minutes, after twenty minutes and after thirty minutes but the deeper muscle is heated less and the gradient is reversed. With microwave director A, comparable rises in temperature occur but peak temperatures are reached in twenty minutes. With a microwave director of type C, the highest temperatures are reached in ten minutes and higher temperatures are reached at all depths in the tissue levels than are reached with short-wave diathermy or with a director of type A.

The relationship between temperatures of deep muscle and subcutaneous tissue after microwave diathermy was different from that after short-wave diathermy (Fig. 10). With short-wave diathermy, the rise in temperature of deep muscle, in comparison to the rise in temperature of subcutaneous tissue, was less than was the comparative rise when microwaves were employed.

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Development of an Impedance Matching Transformer to Increase Heating of Deeper Tissues

We were aware of the fact that because of high reflection at the surface of the skin, the heating efficiency of the electro-magnetic waves we were using is low. To make the transfer of energy from air to tissues more efficient, an impedance matching device or "transformer" was designed by Herrick and her associates [18]. This improved considerably the heating of subcutaneous tissues, muscle and bone. It was concluded that the device would increase the transfer of thermal energy to the tissues and might also make it possible to heat selectively small portions of tissue. Impedance matchers made of the dielectric mycalex, or of mycalex and polystyrene, were tested and proved satisfactory for this purpose. 69 observations were made on 9 normal men [19]. For impedance matching, a cylindrical block of mycalex with a dielectric constant of 8·0, a diameter of 5·08 cm. and a thickness of 10·32 mm. was placed on the skin in the microwave field. In one series of observations, after irradiation for one minute at a plate current of 100 milliamperes, there was an average rise of cutaneous temperature of 1·08° C. at the point not covered by the mycalex cylinder and, at the point covered by the mycalex cylinder, there was an average rise of cutaneous temperature of 2·35° C. In another group, there was an average rise in temperature of muscle at a point not covered by mycalex of 0·70° C. and at the point covered by mycalex the average rise in temperature of muscle was 2·21° C.

A few experiments also were performed in order to determine the change in temperature of the mycalex cylinder when it was exposed to the microwave field. When the cylinder was placed at a distance of 4 cm. from the director, the maximal recorded rise in temperature, either on the surface or in the substance of the cylinder, was 0·1° C. after one minute of irradiation at a plate current of 100 milliamperes.

It was apparent that significantly higher temperatures are recorded in the region covered by a dielectric than in uncovered regions. The dielectric constant of the impedance matcher we used was 8·0. This constant may not be the ideal one and material with different dielectric constants may result in even higher transmission of energy from air to the tissues. We concluded that impedance matching by placing of an appropriate dielectric between air and tissue can be used to decrease the amount of microwave energy reflected by tissue. Further, we concluded that by choice of certain combinations of current intensity and duration of irradiation, some regions might be heated satisfactorily while adjacent regions received relatively little heat.

Studies of Dielectric Constants of Various Tissues at Various Microwave Frequencies

Having proved that microwave diathermy was effective in heating certain localized portions of the body, we wished to explain if possible the experimentally observed temperature distribution produced in the tissues by microwaves. Therefore, Herrick and her associates [20] studied the dielectric constant and loss of freshly excised samples of various tissues. The objective was to increase our understanding of the heating of these tissues. The amount of heat developed in animal tissues from microwave diathermy is dependent on the dielectric properties of the tissues. If these properties vary with the frequency, it is desirable to measure them at the actual frequencies we are using. The dielectric properties of certain body fluids were also studied. These studies aided in the designing of an impedance matcher for increasing the transfer of microwave power into a particular tissue, such as muscle.

The equipment employed for measuring the dielectric constant and loss was a special microwave dielectrometer which was designed by Dr. D. J. Jelatis. Accurate determinations of the dielectric constant and loss revealed varying figures for different types of tissue (Table I). It is hoped that these determinations will be helpful to others in future studies.

Table I.—Dielectric Constant and Loss Factor as Determined* with the Microwave Dielectrometer Designed by D. J. Jelatis

Material	Dielectric constant K	Loss factor Tan δ
Muscle	48	0·29
Fat:		
Homogeneous	3·9	0·17
More fibrous	7·2	0·19
Bone	7·5	0·13
Tendon	32	0·46
Marrow:		
Red	7·1	0·20
Yellow	4·2	0·20

*Determinations made on different tissues of the horse.

The dielectric properties of tissue important in microwave diathermy also were studied at various frequencies (Table II). There were considerable differences in the results obtained at 1,000, 3,000 and 8,600 megacycles.

TABLE II.—DIELECTRIC PROPERTIES OF VARIOUS TISSUES IMPORTANT IN MICROWAVE DIATHERMY

		Frequency and electrical data					
		1,000 Mc. per sec.		3,000 Mc. per sec.		8,600 Mc. per sec.	
Material	Temp. °C.	K	Tan δ	K	Tan δ	K	Tan δ
Muscle:							
Horse	38	52	0·49	48	0·29	43	0·42
Dog	38	52	0·44	37	0·30	40	0·45
Fat of horse:							
Homogeneous	38	3·8	0·33	3·9	0·17	3·9	0·22
More fibrous ..	38	7·5	0·36	7·2	0·19		
Fat of dog ..	38	5·3	0·29	3·7	0·17	3·5	0·16
Bone of horse ..	Room	8·0	0·11	7·5	0·13	8·0	0·17
Tendon of horse..	Room	39	0·37	32	0·46		
Marrow of horse:							
Red	Room	7·8	0·23	7·1	0·20	7·2	0·51
Yellow.. ..	Room	4·3	0·18	4·2	0·20	4·3	0·24
Skin of dog ..	Room	35	0·31	34	0·28	28	0·49

EFFECT OF MICROWAVE DIATHERMY ON BONE, BONE-MARROW AND ADJACENT TISSUES

Next, Dr. Joseph P. Engel [21], also a Fellow in Physical Medicine, investigated under our guidance the effect of microwaves on bone, bone-marrow and adjacent tissues. Our purpose was to study the temperature relationships between bone and soft tissue following microwave diathermy and to investigate the effects of daily exposure to microwaves for prolonged periods. Osborne and Frederick [22] produced with microwaves average temperatures of 105·1° F. in the frontal sinuses of dogs, using a director of type C. This was an increase of 10° F. more than the control temperatures.

Furthermore, studies on dead tissues have indicated that the temperature of bone could be increased with a frequency of 2,450 megacycles but not to the high levels produced in soft tissues, and it was postulated that the exceedingly low dielectric constant of animal bone-marrow would prevent absorption of any measurable amount of energy, so that little or no increase in temperature would be obtained.

In our studies, microwave diathermy was applied to the legs of anæsthetized or trained dogs and measurements of temperature were made before and after irradiation by means of thermistors and thermocouples placed in the adjacent soft tissues and in the cortex and bone-marrow of the upper third of the tibia. When bone was exposed to microwaves for thirty minutes, in such a way that muscle lay between the bone and the source of radiation, the locations of the thermistors and thermocouples, and the direction of irradiation, were as shown in Fig. 11A. Under these conditions, average increases of temperature were as follows: subcutaneous tissues, 4·3° C.; overlying tibialis anterior muscle, 4·6° C.; tibial cortex, 3·8° C., and tibial marrow, 3·0° C. (Fig. 11B.) The rectal temperature is given only to show how the entire body presumably reacted.

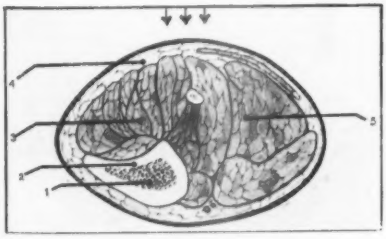


FIG. 11A.

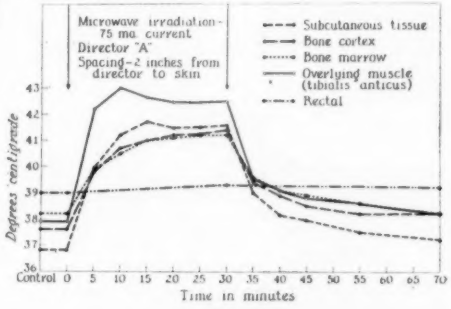


FIG. 11B.

FIG. 11A.—Transverse section of the hind leg of the dog 1·5 cm. below the tibial tuberosity, showing the position of each thermistor when temperatures were observed. Arrows indicate the direction of irradiation on the lateral aspect of the leg when muscle lay between the source of radiation and the bone being studied; 11B.—Temperatures produced in the lateral aspect of the hind leg of the anæsthetized dog after varying periods of microwave diathermy. The cooling curve begins after thirty minutes of exposure.

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When subcutaneous bone was exposed to microwaves for thirty minutes, in such a way that skin and subcutaneous tissue lay between the bone and the source of radiation, the arrangement of thermistors and thermocouples, and the direction of irradiation, were as is shown in Fig. 12A. Under these circumstances, the average increases of temperature were as follows: subcutaneous tissues, 4·1° C.; tibial cortex, 5·0° C.; tibial marrow, 3·4° C.; adjacent gastrocnemius muscle, 4·3° C. (Fig. 12B). No comment is necessary concerning the temperature of tissue beneath bone or concerning the rectal temperature.

When an impedance matching transformer was placed in the field of microwave radiation, there was an increase in the temperature of tissues of approximately 300% over the values

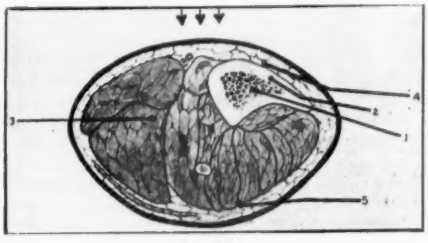


FIG. 12A.

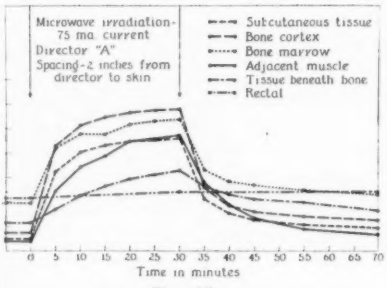


FIG. 12B.

FIG. 12A.—Transverse section of the hind leg of the dog 1·5 cm. below the tibial tuberosity showing the position of each thermistor when temperatures were observed. Arrows indicate direction of irradiation on the medial aspect of the leg when skin and subcutaneous tissue lay between the source of radiation and the bone being studied; 12B.—Temperatures produced in the medial aspect of the hind leg of the anæsthetized dog after varying periods of microwave diathermy. The cooling curve begins after thirty minutes of exposure.

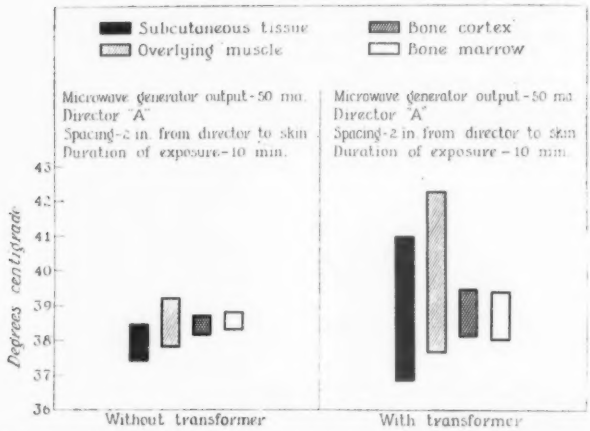


FIG. 13.—Effect of an impedance matching transformer on the temperature of bone and adjacent tissues of the trained dog, when only skin and subcutaneous tissue lay between the bone and the source of radiation.

obtained when no transformer was used (Fig. 13). When skin, subcutaneous tissue and a layer of muscle lay between the bone and the source of radiation, the increases in temperature of bone cortex and bone-marrow were considerably less than the increases in temperature of subcutaneous tissues and overlying muscle. When the microwaves were applied to bone, and only skin and subcutaneous tissue lay between the bone and the source of radiation, significant increases of temperature were produced in bone cortex and bone-marrow without the transformer being in use. Marked rises of temperature occurred when the transformer was used.

Repeated daily exposure of the leg of the dog to microwaves with a director of type A at a distance of 2 in. (5·08 cm.) and a power output of 65 watts, for forty-five minutes during a period of eight weeks, produced no significant changes in the hæmatocrit reading, concentration of hæmoglobin or blood cell counts. However, repeated exposure to microwaves caused more rapid healing of the surgical wounds in the soft tissue than occurred in the absence of such exposure.

Five dogs gave roentgenologic evidence that, under treatment with microwave diathermy, an artificially produced defect of bone filled in earlier than did a similar defect in the opposite untreated leg which served as a control.

Effects of Microwave Diathermy on the Eye

Next we studied in the laboratory the effect of microwave diathermy on enucleated eyes and on the eyes of intact animals. Daily, a Fellow in Ophthalmology of the Mayo Foundation, and his associates [23] determined the changes in the temperature of orbital tissues and aqueous and vitreous humours of the eye after exposure to microwaves. Different distances of the director from the eye, exposures of various durations and power outputs of the generator of various intensities were used. Ophthalmoscopic studies were made before and after exposure; and after enucleation, histologic sections and microscopic examinations were made.

It was known that microwaves would be likely to heat the eye to high temperatures and that, in excessive doses, damage might be done. It was apparent also that the distance of the director from the eye was an important factor in dosage.

Repeated exposures for thirty minutes every other day with a generator output of 94 watts at a distance of 5 in. (12·70 cm.) produced no observable pathologic effects. Daily exposures under the same conditions at a distance of 3 in. (7·62 cm.) produced no observable pathologic effects. However, one exposure for thirty minutes at a generator output of 94 watts, and at a distance of 2 in. (5·08 cm.) produced cloudiness of the cornea twenty-four hours after exposure, and the pupil was half dilated and unreactive. But the eye of another dog treated in exactly the same fashion once daily for ten days sustained no clinically observable pathologic effects. Corneal clouding developed in the eye of a third dog so treated for eight days and, six days after the last exposure, an anterior cortical rosette cataract was observed and a posterior cortical cataract developed later.

Corneal clouding developed in the eyes of two animals which were exposed to microwave radiations with a generator output of 122 watts and at a distance of 1½ in. (3·81 cm.). In an eye of one of these animals, an anterior cortical cataract, and later a posterior cortical cataract, developed. Similar damage to the eye was reported by Salisbury and his associates [12] as a result of experiments performed on rabbits. They found that cataracts were formed on exposure for ten minutes at a field intensity of about 3 watts per square centimetre and at a wavelength of 12 cm. These cataracts developed three to ten days after exposure.

It is evident that microwave diathermy should be applied with extreme caution in the region of the eye. Otherwise cataracts, such as are represented in Fig. 14A and B, will be produced. It is apparent, however, that the eye can be readily screened from microwave radiations and we are planning to investigate suitable methods of screening it. Likewise, with proper use of an impedance matching transformer, regions near the eye could be heated, with minimal heating of the eye itself.



Fig. 14A.

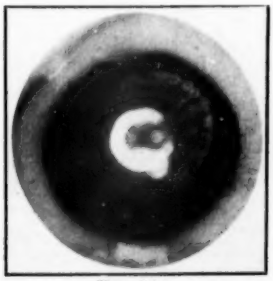


Fig. 14B.

Fig. 14A.—Cataract produced in the eye of a dog following exposure to microwave diathermy.
Fig. 14B.—Cataract produced in the eye of a rabbit following exposure to microwave diathermy.

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Effect of Microwave Diathermy on the Circulation of Blood and on Temperature of Tissues of Normal Human Beings

Once we had completed thorough studies of the effect of microwave diathermy on laboratory animals, we turned our attention to its effect on normal human beings. Dr. J. W. Gersten, Fellow in Physical Medicine, collaborated with us [24] in determining the effect of various outputs of microwaves, and of different periods of exposure to microwave diathermy, on the peripheral circulation and on the tissue temperature in the exposed limb of man. Fifty normal human volunteers were studied. For the temperature studies, thermocouples were placed on the skin, in the subcutaneous tissues and in the muscle at a depth of 1·5 cm. The studies on the flow of blood in the human subjects were done on the exposed and on the contralateral extremity with a venous occlusion plethysmograph and compensating spirometer recorder [25]. The output of the generator was either 60 or 80 watts and the duration of exposure varied from one to thirty minutes. After control measurements of flow of blood and temperature had been established, the forearm was exposed to microwaves and the studies on flow of blood and temperature were repeated after the microwaves were turned off.

Significant increases in flow of blood and in temperature of the tissues were produced in the extremity exposed to microwaves. Changes in bodily temperature, heart rate and blood flow in the unexposed extremity were insignificant. The average rise in temperature of muscle (Fig. 15) was significantly greater than that of the subcutaneous tissues, while the

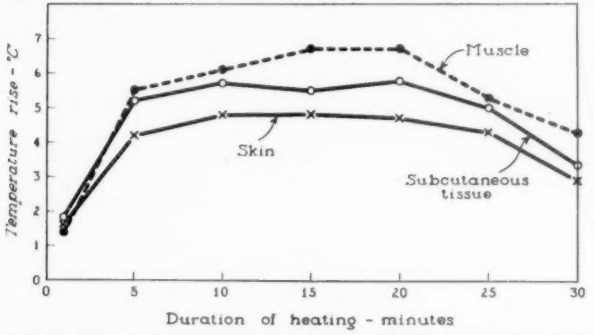


Fig. 15.—Effects of exposure to microwaves (80 watts) on temperature of tissue of the treated extremity. Readings of temperature were taken one minute after microwaves had been turned off. Each point is the average of ten to twenty-six observations.

average increase in the subcutaneous temperature was greater than that of the skin. After twenty minutes of irradiation with an 80 watt output, the increase of temperature was 6·7° C. in muscle, 5·8° C. in subcutaneous tissue and 4·7° C. in the skin. Although the temperatures decreased after twenty minutes of exposure (Fig. 16), the flow of blood continued to increase and reached its height after thirty minutes of exposure, at which time

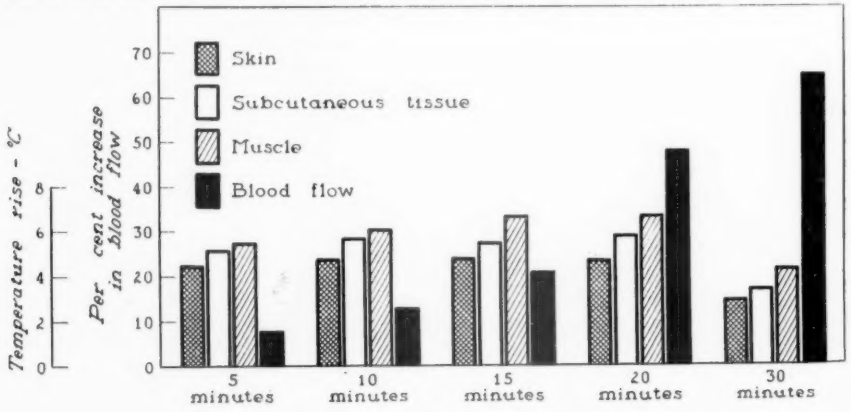


Fig. 16.—Effects of exposure to microwaves (80 watts) on blood flow and on temperature of tissue in the treated extremity. Readings of blood flow were taken five minutes after the microwaves had been turned off. Readings of temperature were taken one minute after the microwaves had been turned off. The height of each bar represents the average of nine to twenty-six observations.

the average increase had reached 65%. It was interesting to observe that after thirty minutes of heating, the decline in the temperature of the tissue from the peak attained at twenty minutes was directly proportional to the increase of flow of blood during the same period.

Deleterious Effects of Excessive Doses of Microwave Diathermy

Certain deleterious effects of microwave diathermy have been noted. Wise, Castleman and Watkins [26] showed that when heavy doses of microwaves were employed, doses sufficient to cause injury to soft tissues, shortening and deformity of bones, or partial or complete epiphyseal destruction, might occur. They concluded, however, that when used in clinical dosage, there was no appreciable effect on growth of bone.

Richardson, Duane and Hines [27] confirmed the observations that microwaves, when applied to the eye at a power output of 100 watts and at a wavelength of 12 cm., for fifteen minutes, would produce cataractous lenticular opacities. Then Feucht, Richardson and Hines [28] found that microwaves of a wavelength of 12 cm. caused a greater increase in temperature of tissues containing metallic implants than in temperature of control tissues. The increase in temperature was of sufficient magnitude to cause gross damage in the tissue contiguous to the metal and between the metal plate and the surface of the tissues.

Early Studies Concerning Treatment with Microwave Diathermy

After facts had been established and techniques developed by laboratory studies on animals, and by clinical research on normal human beings, we began clinical treatment of a selected group of patients [29–31]. Over a period of approximately two years, 481 patients received a total of 4,807 treatments. The number of treatments per patient varied from one to 110. Duration of a single treatment was from twenty to thirty minutes. An output of 60 to 100 watts was used and in most instances the dosages varied between 80 and 100 watts. The conditions treated with microwave diathermy were mostly lesions of the shoulder, particularly periarthritis, tendinitis with calcification or acute bursitis, since it was thought that this group of conditions could be studied fairly readily. Of all patients treated 76·6 per cent had lesions of the shoulder. Bursitis in other regions of the body, conditions following odontectomy, fibrositis, osteo-arthritis and a few miscellaneous conditions made up the other 23·4 per cent.

Lesions of the shoulder.—Analysis of clinical improvement of the shoulder following treatment with microwave diathermy, massage and exercise was helpful in determining the general clinical results. Periarthritis, subdeltoid bursitis and similar lesions of the shoulder frequently cause limitation of motion at the shoulder joint. Measurement of range of motion in this joint provided an objective method of evaluation, which could be considered together with the subjective findings reported by the patient. Certainly, statistically valid conclusions cannot be drawn, yet the observations are sufficiently extensive to allow some clinical impressions concerning the effect of this type of heating.

Final clinical findings were divided arbitrarily into four categories: no improvement, slight improvement, good improvement and excellent improvement. The shoulders of approximately 72 per cent of the patients who could be traced were placed in the category of either good or excellent improvement. Only slight improvement was obtained by 24% and no benefit by 4%. Our clinical impression is that lesions of short duration, such as acute bursitis, are more amenable to the treatment described than are more chronic disabilities, such as periarthritis of long standing or "frozen shoulder". The results obtained compare favourably with those obtained with short-wave or long-wave diathermy.

A few patients in this series, in addition to the customary supplementary treatments mentioned, previously had received roentgen therapy, injections of procaine, needling of a bursa or manipulation of the involved shoulder.

Minor undesirable reactions were noted in examination of only 16 of the 481 patients, an incidence of 3·3%. Fifteen patients noted increase in pain which could be attributed to the microwave diathermy. The increase in pain was described variously as "drawing sensation", "throbbing", "cramping", "deep pain" or "dull ache". In several instances treatment could be continued simply by reducing the output of the machine or changing the position of the director. The pain of one patient was aggravated equally as much by short-wave diathermy as by microwave diathermy. One patient received a first degree burn about 2 cm. in diameter.

Sixteen patients were treated with both microwave and short-wave diathermy. In comparing the subjective reactions to the two types of diathermy, 9 patients reported that they preferred microwave diathermy. The reasons generally expressed for this preference were that there was less systemic heating and less perspiration, no weight or pressure from the applicator, good relaxation and yet adequate local heating. Most of the 7 patients who preferred short-wave diathermy stated that they felt that they obtained more heat over a larger area.

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Our preliminary survey indicates that microwave diathermy has no striking effect on the absorption of calcium in cases of tendinitis with calcification or in cases of bursitis with calcification.

Following odontectomy.—Thirty-five patients with bilaterally impacted third molars for which removal was indicated were selected for the study [32]. In 19 of the cases, the extent of operation on the two sides was approximately the same. Maxillary and mandibular third molars were removed on one side only at the first operation and on the other side at a second operation. As nearly as possible all factors which would alter the postoperative course of swelling and trismus were kept constant. To determine the effect of microwave diathermy, only one side, following one operation, was exposed to microwaves. Treatment was given for thirty minutes daily on each of the first four days after operation on this one side. Microwave diathermy was not given following operation on the other side. Measurements of swelling and trismus were made postoperatively on both sides. The amount of swelling and also the amount of trismus were measured by means of calipers.

During the second, third, fourth and fifth postoperative days (Fig. 17A) swelling was less severe on the side that was exposed to microwaves than on the side not treated. Trismus was less severe on the third, fourth and fifth postoperative days when the jaw was treated with

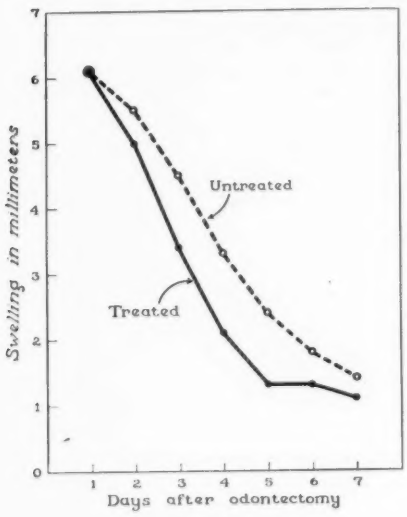


FIG. 17A.

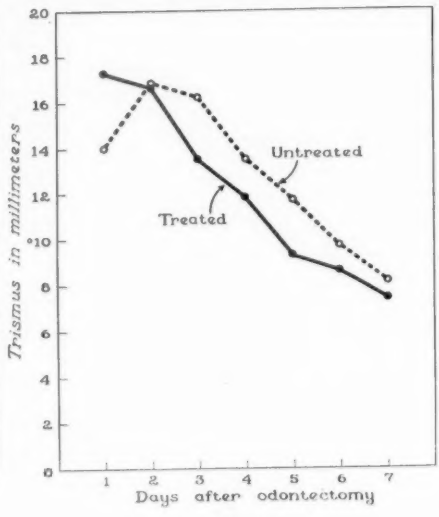


FIG. 17B.

FIG. 17A.—The average degree of swelling of 19 patients as determined by subtracting the preoperative from the post-operative measurement of the distance between lingual embrasure of the mandibular first and second molars and the cutaneous surface of the cheek; 17B.—The average severity of trismus of 19 patients as determined by subtracting the postoperative from the preoperative measurement of the distance between the edges of the maxillary and mandibular central incisors when the mouth was opened maximally.

microwaves following odontectomy than when microwave diathermy was not applied (Fig. 17B). Subjectively, postoperative pain and soreness were relieved, especially during the actual period of heating.

CONCLUSIONS

While more clinical investigations must be done before the exact place of microwave diathermy in clinical practice will be known and until such investigations can be made, microwave diathermy should be employed clinically with caution, nevertheless certain conclusions can be drawn from the studies conducted so far.

It may be concluded that, as have most forms of heat employed therapeutically, so microwave diathermy has certain shortcomings. These include the following: (1) Living tissues may be damaged by excessive doses of microwave diathermy. (2) Ischæmic tissues are especially susceptible to burning by excessive doses of microwave diathermy. (3) Bodily regions containing large amounts of fluid may be heated excessively by microwave diathermy. (4) Tissues overlying bony prominences may be heated excessively by microwave diathermy.

(5) The eye may be damaged and cataracts may be formed by excessive amounts of microwave diathermy. For these reasons, it is concluded that when employed clinically microwave diathermy should be applied with particular caution over or near the following: the eye, ischæmic tissues, regions in which there are effusions, collections of fluid or marked œdema, tissues containing metallic bodies, bony prominences, epiphyseal regions of growing bones or regions in which there are tendencies to hæmorrhage.

Microwave diathermy has a number of advantages over the methods of applying heat locally to living tissues which have previously been employed therapeutically. From our observations it may be concluded that these embrace the following: (1) Microwave diathermy provides a new, extremely flexible and effective means of heating living tissue which permits accurate localization by direction of a beam of energy toward any surface of the body. (2) Absorption of microwave energy is greater than the absorption of energy produced by high-frequency radiations of longer wavelength. (3) Greater rises in the temperature of muscle at a depth of 3 cm., as compared with rises in temperature of subcutaneous tissue, are produced with microwave diathermy than with short-wave diathermy. (4) When microwave diathermy is employed for heating tissues, there is a desirable relationship between cutaneous and internal temperatures which permits adequate internal heating, at least to a depth of 3 cm., without undue heating of the skin. (5) Proper application of microwave diathermy will produce marked and readily controlled or modified increases in the temperature of subcutaneous tissues, muscle, bone cortex and bone-marrow. (6) Microwave diathermy will not only increase the temperature but also will produce marked increases in flow of blood in tissues to which it is applied in experimental animals and in man. (7) Microwave diathermy will produce heating of local regions with almost no systemic heating. (8) Microwave diathermy can be employed clinically for effective heating of local regions of the body and it can be applied with maximal comfort to the patient.

Finally it may be concluded that the use of an impedance matching transformer during applications of microwave diathermy will decrease reflection of radiation by the skin and result in greatly increased transmission of energy to the deeper tissues. Thus, use of the impedance matching transformer provides a new and effective method for accurate localization of heat in deeper tissues.

It can be concluded that because of accuracy of localization, great flexibility of application and extreme effectiveness in production of heat at depth, microwave diathermy may well become a valuable new therapeutic agent.

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Section of Laryngology

President—R. D. OWEN, B.Sc., F.R.C.S.

[*February* 3, 1950]

Transantral Neurotomy and Sealing of the Foramen Rotundum for Neuralgia

By W. O. LODGE, M.D., F.R.C.S.Ed.

UNDER general anæsthesia the alveolar margin and canine fossa are infiltrated with a solution containing one part in ten thousand of adrenaline, the effect upon the pulse-rate being observed.

The anterior antral wall is removed as in the Caldwell-Luc operation. Citelli's bone forceps are excellent for this phase, to gain good access. Even with further use of adrenaline, suction is essential. For removal of the posterior antral wall, sphenoidal sinus intruments are essential. It would be of great value if instrument makers would make a punch of exceptional slenderness designed especially for this operation. An electrical bone drill is serviceable. The posterior antral wall is not thick, but gains strength from its conical form. The antral mucosa, osseous wall and the dense layer of fascia which lies behind it are excised in turn, exposing the contents of the sphenopalatine fossa embedded in fatty tissue (Fig. 1). It must be remembered that this surgical "No man's land" has seven apertures.

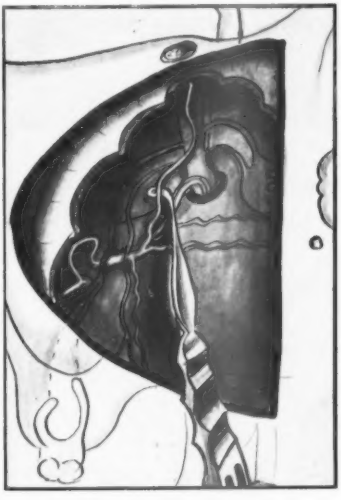


FIG. 1.—Concept of contents of sphenopalatine fossa superimposed upon outlines of the sphenoid bone, viewed through the maxillary antrum. On the hook is the infra-orbital artery. To the left of the eye of the hook are the posterior superior dental nerves and to the right the foramen rotundum, maxillary nerve and sphenopalatine ganglion. Further dissection must precede cutting through the maxillary nerve and curetting out the foramen rotundum with a conical burr.

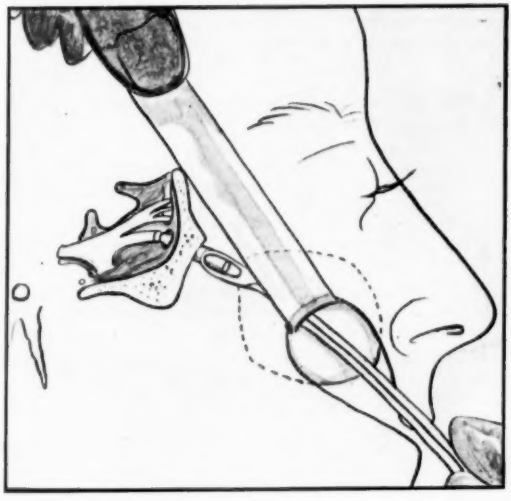


FIG. 2.—Central insert showing the introduction of a costa cartilaginous graft into the foramen rotundum to prevent regeneration of the nerve, orientated upon a lateral view of the face, with upper lip retracted, to show transantral approach. One motive for sealing the foramen is hypothetical; the aim is to block antidromic impulses which lower the threshold of pain.

Lantern slides illustrating the resultant zone of anæsthesia were shown at the meeting.

In the treatment of maxillary neuralgia, that is, of trigeminal neuralgia mainly affecting the maxillary division of the nerve, the advantages of this procedure are simplicity, safety and permanence.

To isolate the sphenopalatine ganglion, a dissecting microscope of self-luminous type is swung into position. To ligate the internal maxillary artery or its infra-orbital branch is good practice. To find the foramen rotundum, I used to pull down the infra-orbital nerve, but no

longer find this necessary. Instead, I identify the lower border of the orbital surface of the sphenoid, which leads to the vicinity of the foramen. The sphenopalatine ganglion is left in situ.

Maxillary neurotomy is next performed, and the foramen rotundum is curetted with the aid of a conical burr such as that used for the Eustachian tube sometimes in radical mastoid operations. Sealing of the foramen may be accomplished by autogenous grafts collected during the operation of access, or else of costal cartilage (Fig. 2). An alternative plan is to insert into the foramen rotundum a vitallium screw, with the aid of an automatic screw-driver. By such means, regeneration of the nerve is prevented. Any fascial or mucosal flaps are replaced and the antral cavity is packed with medicated gauze, my preference being for tinct. benzoin because of its pleasantly deodorant properties; the pack is removed in thirty-six hours from an opening made for the purpose beneath the inferior turbinate, otherwise the gauze might be overlooked; it is from this consideration and to forestall complications that the Caldwell-Luc operation is completed. A course of systemic penicillin is indicated.

After operation, anæsthesia is complete, but pain may persist for a while. Eventually, permanent relief is obtained. Successful cases, with brief case histories, have been shown at meetings of medical societies at Leeds and elsewhere. This is a preliminary communication. The advantages of the procedure are simplicity, safety and permanence.

The following speakers contributed to the discussion on Mr. Lodge's paper:

The President (Mr. R. D. Owen). Mr. J. C. Hogg. Mr. C. Gill-Carey. Mr. E. D. D. Davis. Mr. Wilfred Harris.

Mr. Lodge, in reply, said that it was Albert Carless who had suggested plugging the foramen with rubber or metal from within, about thirty years ago.

A healthy antrum resisted infection: successful cases had been shown at Leeds.

With regard to ligation of the maxillary artery for epistaxis, he submitted that the vicinity of the sphenopalatine foramen was the site of election for two reasons: first, the free collateral circulation and secondly, a rare abnormality—the ophthalmic artery was sometimes found to spring from the middle meningeal, according to Testut (1949).

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Laryngoceles in the Human

By KENNETH HARRISON, F.R.C.S.

REPORT ON FIVE CASES

A LARYNGOCELE is an anomalous air sac which develops from the saccule of the laryngeal ventricle, and is lined with mucous membrane.

Classification.—A. Internal—those lying medially to the thyroid cartilage within the laryngeal cavity. B. External—presenting externally, as a lateral swelling in the neck. C. Mixed—which is combined Internal and External.

Five cases were described, three of the mixed type, one bilateral external and the other internal.

The clinical features were then presented of a typical mixed laryngocele. The patient was an express engine driver, aged 57. He complained of:

(i) Swelling in the neck, in the region of the upper border of the thyroid cartilage (Fig. 1), which presented itself during acts producing great increase of intralaryngeal pressure, e.g. working the regulator on his engine. The size was variable. It was possible to reduce the swelling by pressing on it, and its disappearance was always accompanied by a gurgling sound.

(2) Voice changes. The voice was usually hoarse and frequently weak when the swelling was present.

(3) Shortness of breath, and inability to exert himself when the swelling was present.

On laryngeal examination before the neck swelling was inflated, there was a smooth fullness of the ventricular band; after inflation there was a very marked swelling of the ventricular band, hiding the vocal cord (Figs. 2 and 3). This swelling interfered with the cord movements.

THE GENERAL FEATURES OF LARYNGOCELES

Incidence.—These are not so rare as has been previously thought, and they are often overlooked.

Ætiology.—There may be predisposing and exciting factors.

The *Predisposing* causes may be: (*a*) The presence of a congenitally long saccule, in which it extends beyond where it can be supported by the sphincteric action of the thyro-arytenoid muscle. This view was put forward by Lindsay in 1940. (*b*) There may be a reversion to the presence of an air sac as in members of the Ape family.

The *Exciting* factor, in which there is a great increase of intralaryngeal pressure which may occur during coughing, playing a wind instrument, or during strenuous muscle movements of the upper extremities.



FIG. 1.—Shows the swelling in the neck presenting in the region of the superior cornu of the thyroid cartilage.

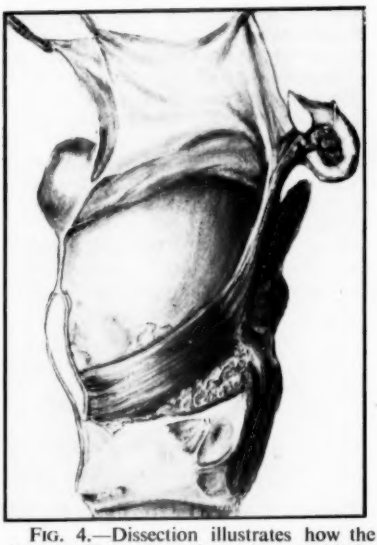


FIG. 4.—Dissection illustrates how the thyrohyoid membrane is continuous with the inner and outer layers of perichondrium covering the thyroid ala. The perichondrial layers have been elevated and are held upwards with forceps. The pharyngeal mucosa is exposed. It is in the tissue plane, between the thyrohyoid membrane and the pharyngeal mucosa that the laryngocele passed upwards. (Drawing by D. Davison.)

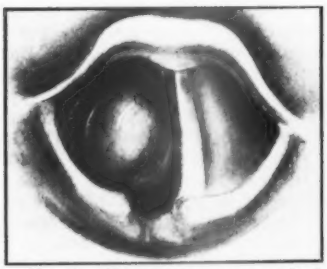


FIG. 2.—Illustrates a very marked swelling of the right ventricular band, when the neck swelling had been inflated.



FIG. 3.—Shows the outline of the laryngocele after injection of 20 c.c. pyelosil.

During these actions, the glottis is closed. This is brought about partly by closure of the true cords, but to a much greater degree by the action of the sphincteric muscles surrounding the upper opening of the larynx, namely the thyro-arytenoid, thyro-epiglottic and aryepiglottic muscles. The glottis is closed to prevent escape of air, the intratracheal pressure is increased, and this is transmitted to the ventricles, apparently because the true cords afford less resistance than the contraction of the sphincter muscles.

Pathology.—Laryngoceles may be unilateral or bilateral. From my observation, the laryngocele swelling is present between the perichondrium lining the medial side of the thyroid ala and the ventricular band. It then enlarges in an upward direction, and on reaching the upper border of the thyroid cartilage, comes to lie deeply to the thyrohyoid membrane.

The thyrohyoid membrane is continuous with the perichondrium covering the thyroid cartilage; they form a continuous sheet of fibrous tissue, and cannot be separated (*see* Fig. 4).

The fibrous thyro-hyoid membrane between its median and lateral ligamentous thickenings is not so weak as is often described.

Many accounts state the laryngocele actually herniates through the membrane, but from my personal observation the sac passes upwards deep to the membrane, as there is no obstruction to its progress. The swelling eventually passes into the more superficial structures of the neck, deep to the lateral border of the thyrohyoid membrane. In this region, there is a dehiscence between the edges of the middle and inferior constrictor muscles, and I consider this is the point through which the laryngocele passes. Once the swelling has passed superficially between these muscles, it may more readily increase in size.

The complication of infection, according to Shambaugh, occurs sooner or later. It usually happens during an acute throat infection, and remains chronically infected. The infected sac may suddenly distend, and there is a danger of sudden death from suffocation. Cases of this nature have been reported.

In our engine driver, the intralaryngeal swelling became quite large when the whole laryngocele was inflated and the patient became quite dyspnœic. It made one think of the potential dangers of such a swelling in the region of the glottis.

Surgical Treatment of Laryngocele

By H. P. Lawson, F.R.C.S.

Operations on *three* laryngoceles have been carried out, and the surgical experience based on so few cases is only mentioned now, in order to complete the histories already referred to.

It must be remembered that though laryngocele is rare, indication for surgical treatment is rarer still. *Only laryngoceles causing distress to the patient require operation.*

Symptoms of distress may be due to (1) distension of the sac internally into the larynx possibly with dyspnœa, (2) difficulty in reducing the distended sac due to valvular action on its neck; (3) infection of the sac; (4) effects of the patient's occupation on the sac.

Case I.—The first laryngocele operated on was in a young man of 21 years, of poor physique, who was a professional trumpet player. He had become aware of a swelling on each side of his neck when attempting to play, and the more strenuously he blew the larger it became. When seen, a bilateral laryngocele was obvious, and this was confirmed by X-ray.

Operation.—This was carried out under intratracheal anæsthesia of nitrous oxide and oxygen, with a little trilene, after the usual premedication; the patient having also been kept under a penicillin umbrella for two days previously. A collar incision was used as it was thought that it might be possible to remove both laryngoceles at one operation, but this idea was soon abandoned as unwise, a view confirmed by Dr. Barretto, of San Paulo, Brazil, who is experienced in these cases, and was present at the operation; therefore the right side only was proceeded with. After the thyroid ala was exposed, an incision through the perichondrium at the upper border of the ala was made, and an elevator inserted between the medial aspect of the thyroid cartilage and the medial perichondrium, separating this layer along the whole length of the cartilage. The cartilage was then divided from above downwards, so that it could be hinged outwards and backwards on the two cornua. In the first two cases, the line of section in the cartilage was made at the junction of the anterior and middle thirds and the anterior third left in situ. This I think was a mistake as the access to the neck of the sac was somewhat restricted, and later it was found that on returning the posterior part of the cartilage to its place, the two fragments did not lie together in good apposition, but tended to override. The internal perichondrium was now exposed, but no sign of the neck of the sac was seen, as this lay deep to the perichondrium. The thyrohyoid membrane was next well exposed, but again no sign of the sac was seen. At this stage the anæsthetist was asked to close his expiratory valve, and as the mouth was packed off with gauze, the sac gradually distended, and it was seen that the portion of the sac lying lateral to the edge of the thyrohyoid membrane was most easily identifiable. This observation confirmed the opinion previously given by Dr. Barretto, that the laryngocele is most easily excised from the fundus to the neck, and not vice versa as would be expected. By occasional inflation with air the dissection of the sac from the apex to the neck was not unduly difficult.

The walls of the sac were quite tough as no infection was present, and the thyrohyoid membrane and internal thyroid perichondrium were dissected off without injury to the sac, by gauze dissection. The neck was found to be narrow and fibrous, and led without doubt into the laryngeal ventricle. Having freed the laryngocele down to the laryngeal sinus, the neck of the sac was clamped and divided as in an appendicectomy, and the stump tied and invaginated with a suture. The internal perichondrium and thyrohyoid membrane were reconstituted and the thyroid cartilage returned to its normal position, and the wound closed and drained with a rubber dam.

The second laryngocele.—This was on the opposite side of the same patient as the first. The technique was exactly the same as in the first case, and was carried out two weeks afterwards. This was an error of judgment on my part, as the previously divided thyroid cartilage had not joined, and the similar incision in the cartilage on the opposite side left the angle of the thyroid cartilage floating, and unstable, with resultant hoarseness and weakness of the voice which continued for about three weeks. At least eight weeks should have intervened between the two operations.

Case II. *The third laryngocele.*—This was in an engine driver, aged 57. He was a muscular man in excellent general health. The laryngocele was on the right side. Symptoms in this case were partly due to the fact that the sac had become infected, and, just before operation, sterile pus was aspirated from it.



FIG. 1.—Excised laryngocele. Actual size.

Operation.—Owing to the previous infection, this was considerably more difficult than the previous two had been. A *J*-shaped incision was used, and when the thyroid cartilage was exposed and separated from the inner perichondrium it was divided *about a half-centimetre* from the mid-line; this resulted in excellent apposition of the cartilage without overriding when it was swung back at the end of the operation. After hinging back the thyroid cartilage, the neck of the sac could just be defined emerging from the laryngeal ventricle, and lying below the inner layer of the thyroid perichondrium. The sac was slightly distended with air, but separation from the thyrohyoid membrane and inner perichondrium was in this case difficult, because of the adhesions from the previous infection and the marked friability of the sac. A small tear eventually occurred, and was closed with an artery forceps so that inflation could continue to aid dissection; however, owing to the friability the tear extended, and it was decided to abandon any inflation and pack the sac with ribbon gauze. This manœuvre was very helpful, and the tightly packed sac dissected out with ease, and the neck was divided and invaginated as before. The cartilage was replaced and the wound closed. A dam drain was inserted for twenty-four hours. This patient made an excellent recovery, and left hospital on the eighth post-operative day.

After-treatment.—Intravenous glucose-saline was not required in these cases as there was practically no shock. Only fluids were given for forty-eight hours. After that time, soft diets were given with ice-cream. The penicillin umbrella was continued for five to seven days after operation.

Follow-up.—The *first* patient has been seen several times since his operations six months ago. Both vocal cords are moving normally, and the voice is natural. All evidences of the laryngoceles are absent.

The *second* patient operated on only one month ago still has a slight prominence of the right ventricular band, but has no symptoms.

In conclusion, I wish to thank Professor Victor Lambert for his interest and for making the cases available to me for operation.

Retention Cysts of the Larynx[1]

By E. D. D. Davis, F.R.C.S.

The drawing of a larynx (Fig. 1) excised by C. P. Wilson shows an upward extension and dilatation of both saccules which are seen at the upper border of the thyroid cartilage on either side of the mid-line. These distensions should appear in the vallecula or they may pass laterally into the neck. I have seen two more similar cases and all of them had an epithelioma of the ventricular band and vocal cord treated by deep X-ray therapy and laryngectomy. The scarring of the ventricle and its band appears to have caused retention of air in the saccule, hence its distension. Cysts of the neck which contain air when nothing is seen in the larynx and when no connexion with the larynx is established, are more likely to be pharyngoceles than laryngoceles. I have seen one pharyngocele in an old lady who had a cyst in the neck at the anterior border of the sternomastoid and just above the edge of the thyroid cartilage similar to a branchial cyst. She could inflate the cyst by blowing out her cheeks. It was assumed that she had a branchial cyst with a fistula into the pharynx. She refused operation. Irwin Moore (1922) has described laryngoceles and found the records of several cases which were extensions of the saccule.



Fig. 1.—Enlargement of the saccules of the larynx.
No. 167, Ferens Institute Museum. A glass stylet has been placed in the ventricle and saccule.

The retention cysts, mistaken for laryngoceles, have been excised by removing the ala of the thyroid cartilage to completely expose the cyst. This approach gives a more complete exposure and easier dissection than that given by laryngofissure or thyrotomy. The late Wilfred Trotter excised the cysts reported by Tilley and Horsford and I have dissected out two similar cysts in this way. A long incision is made along the posterior border of the ala of the thyroid cartilage. The ala is carefully dissected away from the wall of the pharynx and larynx, keeping as close to the inner surface of the ala as possible. The ala is removed in one piece or by using a punch forceps. The cyst is thoroughly exposed and dissected away without opening the larynx or pharynx. The wound heals by first intention and without trouble.

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Mr. S. W. G. Hargrove disagreed with what Mr. Davis had just said. He had one case of a laryngocele to show. The patient gave a history of some loss of voice for five months, no difficulty in breathing and swallowing. Swelling appeared, was present for three weeks and then disappeared. The voice returned to normal. Later the swelling appeared again and with the reappearance of the

[1]*See* Davis, 1923.

swelling the voice again disappeared. He carried out a more extensive operation than Mr. Lawson or Mr. Harrison, dissecting the laryngocele from its apex to the appendix of the larynx, removing the false cord. During the operation a positive pressure was applied to the pharynx by the anæsthetist so that the laryngocele was inflated, this made the operation very much easier. He continued the dissection of the sac starting at the apex and exposed the laryngocele down to its neck, where it passed through a small hole in the thyrohyoid membrane at the junction of the posterior and middle third of the border of the thyroid cartilage. He removed the whole of the laryngocele, together with the false cord. The specimen of the laryngocele was shown complete with the false cord, the mucous membrane lining of the appendix of the larynx being continuous with the lining of the laryngocele.

Mr. Hargrove showed a slide illustrating the specimen which was removed.

Mr. Harrison, in reply to the discussion, said that from the histories and the physical findings he felt quite convinced that these air sacs were definitely continuous with the laryngeal ventricle. The sacs had been produced by the patients during excess of coughing, when blowing a wind instrument and when using the upper limbs for the fixation of the chest, when he felt that there would be sufficient pressure to produce these swellings. He thought the tomograms were quite convincing of the presence of sacs containing air. In the engine driver, by manipulations on the swelling in the neck, changes were seen in the swelling within the larynx. This was actually witnessed and he felt that they were laryngeal air sacs and not pharyngeal.

He thanked Mr. Hargrove for his remarks. He had done a lot of dissections on the larynx and had found that the thyrohyoid membrane was quite a tough structure, it was not just a soft friable structure as the anatomy books said. He found it difficult to see how a swelling could herniate through it, when there was the tissue plane between it and the pharyngeal mucosa through which the swelling could progress without any obstruction at all. There was the definite dehiscence between the constrictor fibres and it was in close relationship with the lateral part of the thyrohyoid membrane.

Mr. Lawson, also in reply, said that the thyro-arytenoid muscle was seen at operation, with the neck of the laryngocele entering the larynx just above it; it could be felt quite easily. There was no doubt that the neck of the sac did not enter the pharynx but the larynx. The first two cases operated on were not infected and there was no fluid in either of the sacs. The third one was infected and did contain fluid but there was no question of fluid in the sacs removed before they became infected. He agreed that at operation the thyrohyoid membrane was tough and fibrous, it had to be incised with a scalpel to liberate the distended sac, the sac protruded through it as it was incised and became much more prominent. He had noticed that in the three cases the sac did not go through the membrane; it was under the membrane, and came out behind the lateral border.

[*March* 3, 1950]

DISCUSSION ON MALIGNANT DISEASES OF THE NASAL CAVITY AND SINUSES

Mr. F. C. W. Capps: In opening this discussion on the treatment of malignant disease in the nose and paranasal sinuses I am basing my remarks on a series of 71 cases of all types of malignant tumour of these regions seen, and with one or two exceptions treated, in the last twenty years. Most of them were under my personal care from the discovery of the disease but a few came for recurrence of disease treated elsewhere or have been under follow-up observation for a long time in our Clinic, having been successfully treated elsewhere. Survival periods have, with one exception, been reckoned from the dates at which malignant disease was definitely established and treated by us.

The cases were:

Squamous-celled carcinoma	39 (23 F. 16 M.)
Adenocarcinoma	5 (3 F. 2 M.)
Carcinoma of type unspecified and sections not available for revision	10 (3 F. 7 M.)
Sarcoma. Round-celled	3 (3 F.)
Osteoid	1 (M.)
Melanotic	1 (M.)
Osteoclastoma (Myeloma)	1 (F.)
Malignant mixed seromucinous gland tumour	1 (M.)
Angeio-endothelioma	3 (M.)
Recurrent angeioma	1 (F.)
Fibrohæmangeioma	1 (M.)
Carcinoma of septum nasi	5 (1 F. 4 M.)
	71 (35 F. 36 M.)

The small group of cases of septal epithelioma fall into rather special category but the remainder can be considered on common ground.

The high proportion of squamous-celled are in line with the histological findings of other series.

Thus New [1] in 1938 gave a table showing 63 out of 91 primary tumours and 30 of 50 secondary tumours to be squamous-celled carcinomas. Ohngren [2] in 1933 classified 98 of 116 epithelial tumours as squamous-celled. Windeyer [3] in 1943 found 45 out of 75.

This histological finding is now much more usual than in the past and is probably due to a change in the viewpoint of pathologists. Certainly revision of many of our older sections resulted in squamous-celled carcinoma being the ultimate diagnosis. Perhaps it can be explained by the observation of Eggston [4] that in 1 in 5 turbinal bones the epithelium covering them is a mixture of squamous and columnar epithelium and that in old age the ciliated epithelium of the nasopharynx may change to stratified and this change may extend into the nose.

It is unfortunate that the majority of cases are advanced and only seek treatment when they have gross deformity or severe nasal obstruction. Pain is, perhaps regrettably, an early symptom in but few cases. It is therefore surprising that results are as good as they are. Certainly in my experience this is a region in which, after the larynx, malignant disease remains localized longer than elsewhere in the upper respiratory and alimentary tracts and if only the elderly and hitherto healthy patient and his doctor were as concerned with the onset of trigeminal pain, one-sided nasal obstruction, hæmorrhage or purulent secretion as they are with the loss of voice we might get our cases earlier and still further improve our results.

Opinions differ as to early or late metastasis in glands or distant areas. Harmer [5] stated that it is late. New holds it to be early. Butlin [6] said: "The rule, however, is that the tumours of the antrum either do not affect the glands or only do so when the disease is very advanced." Windeyer found glandular metastasis in 32·7% of 153 cases, and generalized metastasis in 9%. In 5 cases in my series glands in the tonsillar or submaxillary region were noted when first seen, 3 of them squamous-celled carcinoma, and in another squamous-celled submaxillary glands developed later. One case of septal epithelioma had glands when first seen.

Apart from those cases where a tumour or ulcer is strictly limited to the septum nasi, I do not think that the several ingenious-anatomical classifications of the tumours have any influence or are any help in deciding our line of treatment. Roughly tumours start either from above in the ethmoids or from below in or near the alveolus.

In the use of very high voltage X-rays in a number of cases nothing new or spectacular is suggested in the way of treatment. We have, however, established a technique which can be modified to suit any class of case and has yielded a reasonable percentage of success.

The radiotherapeutist and myself have a weekly joint consultative clinic at which all cases as soon as diagnosed, and whenever possible classified histologically, are considered. We do not, however, always wait for the result of a biopsy before starting treatment when clinically there is a strong case for early attack and it should be stressed that sometimes in the absence of a positive biopsy we are prepared to treat a case on our clinical findings alone.

It has been pointed out by all workers that it is important to get a specimen from deep in the growth. The surface may be covered with polypoid and non-invaded mucosa, or there may be such necrosis or secondary infection that a misleading or equivocal report is received. In the highly malignant types of growth the risk of lymphatic dissemination by trauma of examination or biopsy must be taken seriously. Ohngren and others advocate the removal of the specimen by diathermy. I have quite frequently resorted to three preliminary irradiations as a safeguard. New holds the correct procedure to be a frozen section and immediate radical endothermic surgery if the diagnosis is proven.

The differential diagnosis must be made from syphilis (Ohngren insists on the importance of Wassermann or similar serological test on all patients), tubercle, innocent growths, foreign bodies, rhinoscleroma and Boeck's sarcoidosis. In none of our cases however have we had a positive Wassermann.

Good diagnostic X-rays are of the greatest value in aiding our diagnosis and in indicating the direction and extent of our treatment.

A malignant growth usually gives a very dense shadow, usually ill-defined, and in the advanced cases (and unfortunately as has been said before, many are far advanced before they seek opinion) there may be obvious destruction of the bony walls of the nasal passages or maxillary antrum.

I would emphasize that diagnostic X-rays can best help us by indicating every extension of a growth. At a recent discussion on Diagnosis of Tumours of the Jaw by the Radiology Section [7] I was impressed by the varying opinions as to what standard views should be taken. Standard views form an excellent foundation but they should be supplemented by any view, however unorthodox, which will give further information about the ramifications of a tumour.

The value of tomographs has been wonderfully demonstrated by Windeyer and Wilson [8].

The manner in which they show a bone deficiency not seen in ordinary X-rays would appear to make them an essential part of our diagnostic apparatus.

Treatment.—Combined surgery and radiotherapy is now, I think, the almost universally accepted line of treatment. Neither by itself yields such a high proportion of success though naturally there are exceptions to such a generalization.

In highly cellular sarcomas, usually very sensitive in irradiation, I doubt the wisdom of any surgery and in the small group of hæmangeio-endotheliomata, surgery—except for interstitial implantation of radium in one case—was avoided.

Pure surgery is now a thing of the past, though it is amazing to record that Butlin, by local excision or resection of the upper jaw, without the aid of diathermy, transfusion or chemotherapy, achieved two three-year and three over three-year cures in 14 cases. The operative mortality was, at the time, very high, chiefly from loss of blood and chest complications. It was about 30% of 74 cases in the Göttingen Klinik between 1857–96. Nowadays the operative mortality for these growths is small.

Should irradiation precede or follow surgery or should it both precede and follow?

By preliminary irradiation the periphery is shut off and a large growth may be reduced to much more manageable proportions. Sometimes indeed a complete regression of the primary tumour may be achieved by radiation alone.

This was so in 11 cases:

1 well-differentiated squamous-celled carcinoma; alive and well eleven years.
3 squamous-celled carcinoma:
  Child of 8 alive and well ten years.
  Old woman of 82, alive and well three years.
  Old woman of 70, no local recurrence, but died of carcinoma of head of pancreas three years later.
1 Squamous-celled papillary type; nine years alive and well and no sign of recurrence or metastasis.
1 carcinoma, type unknown; alive and well eighteen years. (Treated at Lambeth by the late Dr. Stebbing.)
3 hæmangeio-endotheliomata; 1 alive and well eighteen years, one died after thirteen years, one alive and well four years.
1 osteosarcoma; alive and well eighteen years.
1 osteoclastoma; alive and well fourteen years.

Even if there is not complete regression a growth may be reduced to the state which would have been found had it been seen early. In other words, as sometimes happens in the larynx and pharynx, that area of growth which remains after partially successful irradiation represents the primary lesion before spread to adjacent areas.

Others argue that it is preferable to operate and remove all the growth while it can be seen macroscopically, leaving the subsequent irradiation to destroy the microscopic residue.

Where extensive skin incisions are planned there may be a risk of delayed healing if irradiated before operation. On the other hand I have not done other than sublabial or transpalatal approach for malignant disease in any of this series and have only incised the skin to remove an area involved by the growth.

Certainly irradiation in the presence of gross sepsis is dangerous and either a drainage operation or primary operative exenteration is desirable.

Our choice is for irradiation by deep X-ray (I have never had access to a radium bomb for these cases) followed by diathermy exenteration and, if necessary, intracavitary radium (applied by the now accepted method on the surface of a mould made to fit the cavity, not inserted in the middle of a pack).

We have had no reason to regret our decision. Irradiation by itself is usually inadequate and unless there can be no reasonable doubt, or the patient's condition or age does not permit, the area should be explored through the canine fossa and more often than not sometimes quite unsuspected residual growth will be found.

As no skin incision is involved the surgical exploration can be proceeded with just as soon as the primary erythema and malaise of the deep X-ray therapy have worn off; usually a matter of a few weeks.

Any surgical procedure in these days should be performed by diathermic cutting and coagulation, unless a lateral rhinotomy through the unaffected skin is being performed. Resection of the jaw as such is unnecessary. It often removes much that is healthy and fails to reach extensions to the orbit, pterygo-maxillary fossa, post-nasal space and sphenoid. Diathermy through a proper approach can chase the growth wherever it goes. All tissue to be removed by avulsion should be first coagulated. Personally, I have found a sublabial approach to nasal passage and canine fossa (Denker's) to be adequate for the vast majority, but others prefer wider access, particularly for growths lying high up and far back. There is a definite advantage, if there is no involvement, in leaving as much of the palate as possible,

as it makes the patient's feeding and speech a much more comfortable matter. Even if in cases of doubt, one diathermizes the floor of the antrum with subsequent sequestration of the bone and sloughing of the soft tissues, the initial stages are still rendered much more comfortable. Harmer, however, always advocates removal of half the hard palate. Removal through the nostril alone must always be considered inadequate and unsafe. When the alveolus or floor of the antrum is involved the palate must of course be removed. The whole of the antro-nasal wall is always removed.

With diathermy you can go right to the base of the skull and the risk of sepsis and hæmorrhage is much less than by surgery, while your coagulation goes considerably deeper than its visible extent, a matter of some importance where a free lymphatic drainage is involved. If the orbit has been invaded it should be exenterated. New says: "The loss of an eye or perforation of the cheek are of secondary importance; plastic surgery can repair the deformity." Though not, of course, the sight of an eye, and where there is reasonable doubt it may be justifiable to remove the orbital plate, diathermize the periglobar tissue and hope for the best. Tissue is taken for section whenever suspect, with a view to further irradiation.

Ligature of the external carotid is done by some and regarded as quite unnecessary by others. It certainly will not stop secondary hæmorrhage. I once believed that it reduced the hæmorrhage at the time of the operation if done immediately prior to opening the nose, and so shortened the operation. I now very much doubt if this is so and the finding of the external carotid may itself be very time-consuming. I pack the operation cavity with a bag of oiled silk and fill it with gauze soaked in flavine and paraffin, remove it all in two or three days and start frequent irrigations. I am very impressed with the immediate post-operative obturators made for Windeyer and Wilson and where I remove the palate shall in future make more use of these. Some surgeons still remove the glands of the neck by block dissections, but I think the majority rely on irradiation. In any case the first glands in the chain of lymphatic spread are the unapproachable retropharyngeal group.

The submaxillary and upper deep cervical glands are included in two of the fields used for the irradiation of the upper jaw. This is partly by design, and partly because they lie in the path of the most convenient angulation of the beam. Whether because of or in spite of this it is certainly a fact that we have had a very small number of cases developing glandular metastasis after treatment. Two cases which had submaxillary or upper deep cervical enlargement when first seen, and treated, showed complete regression of the glands and primary tumour and have remained free for five and three years. Certainly if mobile glands develop after the primary growth had been cured one would be tempted to do a block dissection, but this has not yet been my experience.

I am not unduly dismayed by sequestration of bone as I cannot help thinking that the sepsis and subsequent fibrosis may play some part in the final destruction of the tissue metaplasia.

Success with these cases may in no small part be due to devoted after-care. Crusting and sequestra, with its unpleasant ozœna, need constant attention and the control of pain and the maintenance of the patient's morale are of vital importance. Crusts should be gently removed with forceps two or three times a week and lavage before and after all meals or at least three times daily is advisable with a Higginson's enema syringe. The patients can usually do this for themselves.

All the analgesics including physeptone are employed, but aspirin is usually very adequate. Blocking of nerve trunks for pain is not often feasible or successful as the field of approach is usually septic. As a palliative measure for the extensive pain of late growths in the skull prefrontal leucotomy has been suggested.

Radiation cataracts are a frequent sequela. With regard to any subsequent deformities or deficiencies it seems to be generally accepted that cheek, nose, eye socket, &c., are best closed by plastic flaps, but the palatal deficiencies are much better repaired by dental obturators, which it is now possible to make extremely light and which carry teeth.

Defects of orbit or cheek can be covered temporarily with flesh-tinted modelled shields often conveniently attached to spectacle frames.

Results and prognosis.—Both of these have improved very greatly in the last two or three decades. New [9] went as far as to say that in the last fifteen years there had been no greater advance in the treatment of malignant tumours than in that of the upper jaw. Operative mortality is much reduced and more patients are alive without recurrence. Increasingly expert anæsthesia, pre- and post-operative chemotherapy and antibiotics, and transfusion in all its aspects, have contributed greatly to the mortality reduction.

Several of our earlier cases were lost soon after operation from pneumonia and one from meningitis. These are now rare occurrences as all cases are put on pre- and post-operative systemic penicillin as a routine.

New has noted that extensive, primary, highly malignant tumours often give better

results than those of the same size, but of low-grade malignancy. The reason is that radiation treatment will destroy the highly active ones, whereas every particle of low-grade tumour must be removed by diathermy, and this is no easy matter.

Some 1 in 10 cases will lose an eye, either by deliberate design or from subsequent ophthalmitis, and some get a deformity which causes dropping or displacement of the eye and double vision.

In 1947 [10] when this series was much smaller and did not include septal ulcers, 37 of 51 cases had been observed for five years or more and 14 were symptom free for five to eighteen years or 37·8%. This included every type of tumour, only 2 cases were untraced, and all were treated. Of cases classed as carcinoma (of all types) 10 out of 17 were symptom free for five years or more. I felt then that this was too rosy a picture to be sustained.

Taking all cases up to 1946, but again excluding septal ulcers, the figures now are 57 followed five years or more, 2 untraced, 22 symptom free for periods varying from five to twenty years. One lived five years but had active disease most of the time. This gives 38·6% so that the figures are remaining about the same.

A more detailed and satisfactory analysis of cases up to 1946 is shown in the following tables and the overall results with carcinoma do not, as I suspected, look so good. Short-term results since 1946 are again encouraging and if I choose the right moment in the next few years perhaps things will look better.

TABLES OF RESULTS

Squamous-celled carcinoma. 39 *cases.*
Up to 1946. 32 cases.
11 alive five years or more (17.16.13(2).11.9(2).8.6(2).5.) 34·5%.
2 of these now dead, 1 from secondaries developing after nine years free of disease.
1 from leukæmia at age 76, thirteen years after treatment.
1 case untraced.
1 case recorded as a failure had diathermy excision (5 or 6 times) and radium needles, for a swelling of the palate involving the antrum, thirteen years before coming to us with an extensive growth which had given pain for two months.
Since 1946. 7 cases.
Alive without recurrence 5 (four years. 3 years. nine months (3)).

Adenocarcinoma. 5 *cases.*
1 alive and well twenty years.
1 alive and well ten years.
1 died after five years but never free of disease.

Carcinoma type unspecified. 10 *cases.*
1 untraced.
1 alive and well for eighteen years (but not treated by us).
8 dead (2 lived three years with disease, one of them having no treatment).

Carcinoma of all types free of disease five years or more.
54 cases. 2 untraced.
14 of remaining 52 = 26·9%.

Sarcoma.
Round-celled. 3 cases all dead.
1 survived eleven years having recurrence in ribs first year, lower ileum second year, then free for eight years and died of general secondaries.
Osteoid sarcoma alive eighteen years.
Melanotic sarcoma died of general secondaries in a year.

Osteoclastoma.
1 alive and well after fourteen years.

Malignant seromucinous gland tumour.
1 free of disease one and a half years, then for another five years. Died at seven years with recurrences in base of skull.

Angeio-endothelioma. 3 *cases.*
1 alive and well eighteen years. 1 died after thirteen years free of disease (nominally of recurrence but no details were available).
1 alive and well four years.

Recurrent angeioma
1 alive and well after eighteen years.

Fibrohæmangeioma.
1 alive and well thirty years.
All tumours up to 1946. 57 followed for five or more years. 2 untraced. 22 symptom-free five to twenty years = 38·6%.

Of 295 cases in which operation was performed before 1929 in the Mayo Clinic, 236 were traced and 127 or 53·8% were without recurrence five years later. Of apparently primary

tumours (of the antrum) 75 out of 91 were traced and 30 or 40% were without recurrence after five years. Of secondary antral tumours, 43 out of 50 were traced and 23 or 53·4% were without recurrence five years later. Of upper jaw and palate cases 118 out of 154 operations were traced and 74 or 62·7% were without recurrence five years later. In all these there is a fairly high percentage of the untraced, which make the percentage of successes look a little optimistic.

Ohngren records 235 cases in which operation was performed between 1924 and 1936, and gave the end-results in 120 cases in which it had been possible to follow the patients for five years or more. Of these 42, or 35%, were alive and well five to twelve years after treatment (cf. Mayo Clinic, 53·8%; Ohngren had a very small proportion of untraced cases).

Windeyer [8] and Wilson, who traced 97% of their cases, had 18·8% five-year success in 69 cases treated between 1925 and 1935 and 30·8% five-year success in 13 cases treated in 1936 and 1937. Up to 1943 their percentage of three-year successes was rising in spite of the fact that all cases, however advanced, were being treated. Of 9 cases of sarcoma treated prior to 1937, only one, a fibrosarcoma of relatively low malignancy survived symptom-free for five years.

It is not easy to correlate all these but it does look as though 30–40% of success should be possible in clinics with a well-established technique.

Harmer, in his very thorough review of the situation in 1931, recorded 819 cases from many sources and many types of treatment; 427 were dead—136 were lost—207 were alive without disease—63 for five years or over, and 49 were alive with disease. The comparable figure to the other series is 63 symptom-free for five or more years, in 683 cases only about 9%. Perhaps the value of many small series added together with bigger series gives a false picture. The value of team-work emphasized by Windeyer is outstanding, and cases are probably better concentrated into a few well-equipped centres.

Davis [11] reported 50 cases in 1934 and appears to have had only one five-year survival but his experience with the radiation side of the treatment does not seem to have been very happy, and the other side of the picture seems to be shown by Dargent, Gignoux and Gaillard [12] in a series reported in 1949 of 191 epitheliomas and 16 sarcomas with only 24 cases alive after five years and who did not favour electrocoagulation.

I am more than ever convinced that skilled radiation therapy and electrocoagulative surgery combined offer the best hope of success.

Lastly may I make a brief mention of the small series of 5 septal epitheliomata. These I believe to be a problem by themselves. 4 of them were in the vestibule of the nose and arose, I suspect, from skin rather than mucous surface. One of these was a warty growth discovered by accident in a man who came for treatment of otitis externa. A second was a large mass arising just behind the columella, with secondary submaxillary glands. Two were typical everted edged epitheliomatous ulcers, one arising in a case that had had lupus followed by basal-celled carcinoma treated by radium.

The fifth had an ulcer of the septum arising just behind the vestibule and extending back nearly to the posterior choana. He was a man of 65 who complained of right-sided nasal obstruction of recent date and was found to have a large mucous polypus blocking the posterior choana. This was removed under general anæsthesia and the eroded area of the septum which looked like an atrophic condition was biopsied at the same time. It was an anaplastic carcinoma.

The warty growth was treated by a sandwich treatment of radium applicator outside and a tube in the nostril, and completely disappeared. He was followed for two years but cannot now be traced. The man of 68 with the large mass had deep X-ray therapy which resulted in regression of the glands and reduced the mass in the vestibule to a flat area behind the columella which was excised by diathermy. He developed cervical gland and distant metastases and died within a year. The first typical epithelioma was excised by diathermy and appeared to be doing well ten months later. He then failed to return for follow-up and within a few months had extensive glands in both sides of the neck and died.

The woman with lupus-rodent-epithelioma was treated by wide diathermy excision of the tip of the nose and anterior part of the septum, and has remained well for seven years.

The last case was treated by removal of the whole septum through a sublabial incision and diathermic cutting and then by intracavitary radium and deep X-rays to the cervical gland area on both sides. It was only done just over a year ago and appears quite satisfactory but it is much too early to be significant.

These cases seem to metastasize much more rapidly than the antral and ethmoid cases and the proximity of so much cartilage makes them unsatisfactory for teleradiation.

In conclusion I must acknowledge my indebtedness to my colleagues of my own and other hospitals for passing their cases to me, and I would especially like to thank my Registrars past and present for their help in the follow-up work. This, after six years of

war was not an easy matter, and the fact that we have only 2 untraced cases is an eloquent testimony to their labours.

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Mr. I. G. Williams: *Carcinoma of the antrum.*—It soon becomes apparent on reading the case histories of these patients that the signs and symptoms of carcinoma of the antrum are those of extra antral extension, that is of advanced disease. Out of 26 cases seen in the last ten years each one had growth either involving the cheek, the orbit or fungating into the nose or through the palate, and I have never seen a carcinoma of the antrum confined to its organ of origin. The symptoms of early malignant disease in this site do not differ from those of inflammatory antral disease, whilst the frequency of benign conditions compared with the infrequency of carcinoma renders it unlikely that earlier diagnosis can be hoped for. At Barts we see 2 to 4 cases of carcinoma of the antrum out of a total of 2,000 admissions for malignant disease per annum. In spite of the locally advanced state, lymph node metastases are uncommon, 3 out of the 26 had enlarged but mobile lymph nodes, clinically malignant.

All these facts were pointed out by Henry Butlin over fifty years ago.

"The first sign of serious disease," he wrote, "is the appearance of a swelling of the face over the antrum, or a fulness and obstruction of the corresponding side of the nose. With the fulness of the nostril there may be a discharge of bloody fluid. The swelling gradually increases, not only in the direction in which it was first noticed, but also towards the orbit, down towards the mouth, and back into the sphenomaxillary fossa. The eye may be pushed up and the hard palate down, as the disease advances the bony wall may be destroyed, with affection of the soft parts around the bone. The skin of the face in this way becomes adherent to the tumour, and immovable over it, and the result may be a vast ulcer, with the thrusting forth of a fungous mass. The lymphatic glands, whether in front of the ear, or behind and beneath the lower jaw are seldom affected, yet I have seen them enlarged in very rare instances at a comparatively early period of the disease."

"The earliest symptom of the disease may be violent toothache. To relieve this pain one or two teeth may be extracted, and as the apparent result of this extraction or independently of it, a sinus forms. A probe passed into the sinus may strike on crumbling bone, or may pass directly up through the alveolar process into the cavity of the antrum, which may feel as if filled in whole or in part with soft tissue resembling granulation tissue. Even now the nature of the malady may be unsuspected, although the patient's toothache has not been relieved, for it is singularly insidious. The new growth replaces destroyed structures and fills cavities reaching to the base of the skull and yet may present even to close examination scarcely any sign of a tumour. The course of the disease is often so rapid that within a few weeks of the first pain and sign of mischief in the alveolar process, and when there is yet scarcely any sign of actual tumour, it may be beyond the reach of operative treatment. I have myself attempted its removal by complete removal of the upper jaw within seven weeks of the first sign of any affection in the mouth, and have found that the whole of the bone was destroyed, and that the new growth had extended into the neighbouring sinuses, and into the muscles around the upper jaw, so that complete removal was impossible, and I have been present at operations performed on patients whose symptoms dated from only two or three months previously, and yet, in spite of the fact that there was no visible tumour, and the diagnosis was still uncertain, the disease had advanced so far that it was not found possible to remove it."

Butlin recommended total extirpation as the only guarantee of cure. He recorded in 1900, 14 cases that he had operated upon.

Total cases	14		
Died of operation	4	Alive and well within three years ..	2
Died of disease	5	Alive and well more than three years ..	3

These 3 were alive at ten and five years, the third dying of chest disease sixteen years later. Can radiotherapy alone eradicate the disease? We have long survivors. 2 out of these

cases survive six and a half and ten and a half years following high voltage radiotherapy. The ten and a half year case, a man of 50, had a proved squamous carcinoma with a swollen cheek, a bulging maxilla and growth fungating in the middle meatus. He was treated to a dose of 5,000 r in twenty-three days and remains well, apart from a radiation cataract. The six and a half year case was a man of 42 when treated with involvement of the orbit by a squamous carcinoma, but he remains well, again with a radiation cataract as the price he paid. In this case following radiation therapy the bony wall of the orbit regenerated, and I have seen this happen in a further case.

The facts that we have mentioned concerning the invasion of adjacent sinuses and tissues indicate that too often the disease is too extensive for complete extirpation. Success with surgery depends upon the complete removal of the growth, and is dictated by the anatomical extent of the growth, and the mutilation entailed by its removal. The problem with carcinoma of the nasal sinuses resolves itself into eradication of the growth from the antrum, the invaded bony walls, and the infiltration into the soft tissues of the face and deeper sinuses of the skull. Success with radiotherapy depends upon the response of the tumour to the radiations, and this in turn depends upon three principal factors.

(1) The inherent radiosensitivity of the cells.

In the case of the nasal sinuses the commonest growth is a squamous-celled carcinoma of low differentiation and high radiosensitivity.

(2) The tumour bed and an intact vascular supply.

Invasion of soft parts can probably be dealt with, but invaded bone is notoriously more difficult to deal with by means of radiation. It is probably true to say that malignant tissue cannot be destroyed in bone unless you give a necrosing dose, although there are exceptions.

(3) The dose delivered and its even distribution throughout the tumour bearing volume.

The majority of patients thus need combined therapy. A recent case emphasizes the importance of surgery, for following radiotherapy with apparent restitution to normality, on opening the antrum it was found to contain extensive growth.

I believe that *irradiation* should always be carried out before *surgery*. To operate first is bound to mean cutting through tumour tissue, as the growth is almost always involving extra-antral tissue. Irradiation can deal with this. There is then a smaller growth left to deal with, as well as growth in bone, whilst the general effect of the rays on the whole tumour must be to depress activity and render it less likely to spread and metastasize if cut across. These are the advantages to the surgeon. It is also an advantage to the rays to work on a tumour with an intact blood supply—the cutting of blood vessels and the coagulation of others by diathermy diminish the vascularity and hence diminish the response to irradiation.

Type of radiation.—Many institutions in this country are now installing very high voltage X-ray therapy machines. Although these tumours are superficial great advantages are obtained by the use of X-rays generated at one million volts and over.

(1) The presence of the bony wall. Bone absorbs more radiation than soft tissue. Some measurements made by our physicist, Mr. Innes, show that for 200 kV. compared with 1,000 kV. about five times the amount of radiation is absorbed, in other words, screened off by the dense bone before it reaches the soft tissues on the other side.

There is another advantage. With 200 kV. radiation there is an increase in ionization of 2–3 times in a 4 to 5 cell thickness around the bone, that is, there is a very high concentration of dose in the bone and for a short distance around it. This local concentration may be responsible for bone necrosis following radiotherapy, without soft tissue necrosis, which occurs later when the sequestrum has formed. With the million volt the dose is more uniform, and hence the liability to necrosis is not so great.

These factors apply also to gamma-ray therapy. Hence teleradium therapy has the same physical advantages as very high voltage X-ray therapy, provided there is sufficient radium to deliver an adequate depth dose—preferably at least 10 grammes.

(2) The beam with these high voltage machines diminishes much more slowly with distance, that is the dose at 2–3–4 &c. cm. is greater than for 200 kV. This increased depth dose means that simple arrangements when cross-fired will deliver a maximal dose—the maximum being set by the local reactions in the irradiated volume. Greater simplicity means greater accuracy, and a higher degree of efficiency in delivering the dose to the selected place.

(3) The higher depth dose means also that the shortest cut need not be taken to get there, nor the most economical route, which may be through vital organs. Irradiation of both parotid and other salivary glands can be avoided, and thus save the dry mouth, a most unpleasant result of irradiation in this region. With 200 kV. the fall of depth dose is such that in order to get an efficient dose one must go through tissue and organs, where radiation effects produce unpleasant sequelæ.

The surgery is carried out when the reactions from this irradiation are healed—that is some four to six weeks later. If residual growth is thought to be present after full external

radiation and the surgical removal, radium is inserted into the antral cavity on a stent mould. The dose from this central cone of radium is calculated to deliver an extra 3,000 r to 6,000 r in ten to fourteen days at the desired depth depending upon the conditions—each case must be considered on its merits.

The Hazards of Radiotherapy

The hazards of radiotherapy in this region are three in number.

(1) The dry mouth: This occurs when the salivary glands lie within the fields of irradiation and is due to destruction of the glandular elements. It is a most unpleasant sequela because not only is there insufficient saliva to aid in deglutition, but the saliva itself becomes thick and tenacious and cannot be swallowed. Lubrication of food can be assisted by taking some paraffin before meals, and the fields should be planned to avoid as much of the salivary glands as possible.

(2) Bone necrosis: This is due as much to the invasion of bone by growth and the surgical measures undertaken, especially the use of diathermy, as to the irradiation. The use of post-operative radium probably increases the extent of necrosis. The sequestra are slow in separating and this long period can be very painful. It should be anticipated by removal at the primary operation of all bone which is liable to necrose.

(3) Eye damage: The eye has to be included in the fields of irradiation in the treatment of ethmoidal and antrum cancer. The reactions produced are severe primarily and include conjunctivitis in every case, and more uncommonly choroiditis, iritis, and keratitis. These are treated on general lines. More serious are the late sequelæ, chronic conjunctivitis, iritis, and choroiditis, corneal opacity and cataract. The eye thus becomes blind and painful. In our 26 cases, each one had an immediate conjunctivitis, 7 had more severe complications and four survivors have an irradiation cataract. Three of these are symptom-free, apart from a blind eye, but one has a troublesome chronic conjunctivitis and iritis.

All factors should be weighed carefully, the extent of the growth, especially involvement of the orbit, the age of the patient, and an assessment of prognosis to decide whether the eye should be removed before treatment is begun. Radiotherapy is much easier to apply if one is not worried about eye reactions, whilst the frequency of late reactions in our survivors justifies removal. If the orbital plate is destroyed or removed and the eyeball drops down, then if it is allowed to remain down the eye will become blind in any case, although one can fit an obturator with a leg to support the eyeball.

The plan of treatment we adopt is:

(1) Examination of patient and decision whether the eye should be removed.
(2) Pre-operative X-ray therapy with the hardest ray available (million volt or teleradium).
(3) Four to six weeks later, operation.
(4) Intra-antral radium when the primary sloughs have separated, if indicated.
(5) Block dissection of the neck—if indicated.

Results
1939–1949

Total cases treated 26 (21 primary, and 5 recurrence.)

Died 17

Untraced .. 1 Alive and well when last seen two years after treatment.

Alive and well .. 8

Dead:

12 died in the first year, five of these being cases with recurrent disease following other forms of therapy. 2 died in the second year. 2 died in the third year. 1 died of disease in the fifth year.

Alive:

10½ years .. 1 case.
7 years .. 1 case.
5 years .. 2 cases.
4 years .. 1 case.

3 are too recent having been treated in the last two years. 15 cases were treated five years and over and of these 1 is untraced and four are alive and well (27%).

I would like now to describe our experience with two cases of benign vascular tumours, and some tumours of the nasal septum.

(1) Hæmangioma: Female. 36 years old when treated. Diffuse hæmangioma of the nasal cavity, associated with angioma of the face. Repeated treatments over twenty years by cautery and radium for repeated epistaxis. Both external carotid arteries had been tied as well as the anterior ethmoidal vessels and yet the epistaxis was not controlled.

She was treated on the million volt unit to a dose of 2,000 r in seven days. She still gets an occasional epistaxis necessitating plugging but on the whole is improved, and leads a normal life.

(2) Kenneth P., male, aged 15. Nine months' history of nasal obstruction and epistaxis.

7.2.46: Removal of vascular pedunculated tumour growing from basisphenoid. Section: Hæmangio-endothelioma.

April 1946: Radium to residual growth. No effect. Three months later: 1,000 r in seven days. H.V.X.R. Considerable regression but growth still present.

Three months later: Further 2,000 r in seven days. The growth regressed completely. He is left with an atrophic rhinitis which does not seem to worry him very much.

Lastly 11 cases of squamous carcinoma of the nasal passages. In 6 of these the whole nostril was filled with fungating growth. The age incidence of these 6 cases is interesting for the youngest was only 10 years of age, the next was 16, the remaining 4 being 64, 70, 73, and 85 years old. The 10-year-old boy who also had extensive lymph-node involvement died, but the growth, as expected, was very radiosensitive. The 16-year-old boy had a fungating tumour growing from the nasal vestibule with a chain of visibly enlarged lymph nodes on both sides of the neck. The growth was an anaplastic squamous-celled carcinoma. We treated the nose and both sides of the neck with complete regression of the tumour. Nine months later a crusted ulcer appeared extending as a sulcus between the right and left nostril below the columella. Section of this ulcer showed granulation tissue only. Following calciferol therapy the ulcer healed rapidly and he remains well nearly two years later.

Of those in the older age-group—one died very rapidly from an intracranial extension. In another we were completely unable to control the disease. She had three courses of treatment and died within a year. She had a fungating growth involving the septum, the lateral nasal wall and the skin of the nostril, and each time primary regression was excellent.

The other two cases are more cheerful. An old lady of 70 with a massive recurrence filling the nostril following removal of some "nasal polypi" remained well for three and a half years, with normal nostrils. She died from senile decay. The last one with a fleshy growth arising from the basisphenoid was 85 years old, and remains well one year after high voltage X-ray therapy partial removal and a radium applicator.

It therefore seems to be that these fungating nasal tumours arise in the young, i.e. the second decade, and after the sixth decade, that they are highly malignant, highly radiosensitive and that there is hope that radiotherapy can control the disease.

The second type of carcinoma is the small fissured or ulcerative type which arises either at the mucocutaneous junction of the septum and skin or in the vestibule. My first experience with this growth was tragic. They were three men in the prime of life. The first was a man aged 50 with twelve months' history of a sore in the nose. He had a small ulcer just inside the nares, extending on to the skin, which on section proved to be a well-differentiated squamous carcinoma. It was treated as a skin carcinoma, giving 3,000 r to a 3 cm. area in three days. The ulcer healed but one year later there was a perforation through the septum and a nodule of the upper lip. This was treated with a planar radium implant, but eighteen months later he had an ulcerating growth in both nostrils eroding the septum, the premaxilla and the skin of the tip of the nose. This was widely excised and he remains free of recurrence to date.

The second was a man aged 46 complaining of crusting within the nostril of one month's duration (squamous carcinoma). There was a granular area on the front of the septum 2 cm. in diameter. This was treated with a larger field 6 by 4 cm., 3,600 r in fourteen days. He got very sore, but within one month of the reaction healing there was recurrent growth on the septum and a small lymph node tucked below the left mandible. He then had a full course of teleradium therapy to the nose and neck.

In spite of this he got an extensive local recurrence which was widely excised, but he died from his disease, the whole history from first symptom to death being only eight months.

The third case had six weeks' history of nose bleeding and swelling of the nose. He had a polypoid growth filling one nostril and an enlarged cervical gland. We treated him with X-ray therapy with excellent primary response. However, within one year there was a recurrence at the primary site. This was excised but he died three months later from disseminated metastases. The next case was a married woman of 39 with a small excrescence and a tiny biopsy scar on the nasal septum just inside the nares. After consultation we treated her with low voltage X-rays to a high dose, 5,000 r in twenty days. She remains well to date, but it is only one year since we treated her.

Lastly we have one case of carcinoma of the nasal septum who is very well one year following excision and an intranasal radium applicator designed to irradiate the edges of the cut, and especially the upper and deeper part.

Concerning the small tumour which arises at the mucocutaneous junction, I believe that apart from their inherent malignancy these growths are more dangerous because they seemed to infiltrate along the lines of cleavage of the first and second arches, along the line of a hare-lip and deeply into the nostril and that we should be much more radical both with surgery and radiotherapy in dealing with them.

Reference—BUTLIN, H. (1900) The Operative Surgery of Malignant Disease, 2nd ed. London.

The following also spoke:

Dr. Gavin Young. Mr. H. V. Forster. Mr. J. C. Hogg. Dr. N. S. Finzi. Mr. R. L. Flett. The President (Mr. R. D. Owen).

Section of Proctology

President—MICHAEL J. SMYTH, M.Ch.

[*February* 8, 1950]

Carcinoid Tumours of the Rectum

By RONALD W. RAVEN, O.B.E., F.R.C.S.

THIS Section has discussed the subject of carcinoids on three occasions: when Lloyd-Davies demonstrated a specimen of carcinoid of the small intestine, Naunton Morgan demonstrated a specimen of carcinoid of the terminal ileum with a carcinoma of the cæcum, and Cuthbert Dukes made valuable observations on carcinoid tumours of the rectum in 1946.

There are several aspects of the subject which deserve further consideration. The title is unfortunate and misleading; common and accepted usage being responsible for its survival. Controversy has occurred regarding the nature of the tumour, and it is important to recognize its clinical significance and properties. A number of cases of carcinoid of the rectum have been reported initially by the pathologist as adenocarcinoma. The first carcinoid tumour described by Merling over 100 years ago occurred in the appendix and was diagnosed erroneously as a carcinoma.

Distribution.—The tumour usually occurs in the gastro-intestinal tract but is also found in other situations, e.g. in ovarian teratomas in connexion with gastro-intestinal and respiratory tissues. Carcinoid has also been described as one type of bronchial adenoma. Other sites affected include the gall-bladder, Meckel's diverticulum and the mesentery. In the gastro-intestinal tract the tumour occurs most frequently in the appendix, being found there almost twice as often as in the small intestine where it has a predilection for the terminal ileum. Cases are described where the stomach, duodenum and colon were involved. A carcinoid is sometimes part of a multiple tumour complex; thus, Cruickshank and Cunningham, in a series of 17 cases, found this situation in 3; and Morgan (1947) described an interesting specimen of carcinoid of the ileum and fungating carcinoma of the cæcum. Approximately 60 cases have been published of carcinoid tumour in the rectum, and it is interesting to note that the majority have been detected during the last four years.

CLINICAL FEATURES

The cases may be divided into three main groups:

Asymptomatic cases.—The carcinoid is found in the rectum as a result of examination for some other condition such as fissure or hæmorrhoids; it may be an accidental finding in an operation specimen of a rectum removed for carcinoma.

Metastatic cases.—The patient may present with symptoms due to metastases in other organs, especially the liver, the primary growth being silent. Horn described such an occurrence in a woman whose symptoms extended over a period of eleven weeks. Her liver was almost entirely replaced by metastases and she died shortly afterwards of liver failure. Pearson and Fitzgerald reported 2 patients with widespread metastases on admission. The chief symptoms in this group include anorexia, nausea, increasing fatigue and loss of weight.

Cases with rectal symptoms.—The chief symptoms are rectal bleeding, either bright or dark red in colour; a change in bowel habit with constipation of increasing severity, or diarrhœa; and tenesmus. The tumour may be single, and usually arises in the anterior wall of the rectum; it may be completely submucosal, but in other cases there is a partial covering of mucous membrane. It is freely mobile unless infiltrative characteristics have developed. The type is variable; thus, a nodule, polyp, plaque or annular constriction may be felt. The consistency is rubbery or firm, and in some cases there is infiltration of surrounding tissues. In some cases the size may equal any malignant rectal tumour. On inspection the colour varies from white, yellow to red-brown. Rigdon and Fletcher reported a case of multiple carcinoid tumour; there were innumerable nodules of variable size underneath the mucosa. The differential diagnosis depends upon the type of carcinoid present. When pedunculated, it must be distinguished from an adenomatous polyp; if submucous, from benign connective tissue tumours and inflammatory swellings; when it is infiltrative, carcinoma and lympho-granuloma inguinale must be considered.

Case record.—Female, aged 60, complained of continuous pain in the rectum and tenesmus. She had been constipated for years. There was no bleeding or diarrhœa.

Examination.—General condition good ; no physical signs except in the rectum. On rectal examination there was a firm polyp arising from the right lateral wall, 3 cm. from the anus. Large internal hæmorrhoids were also present. Sigmoidoscopy showed no other abnormality up to 20 cm. from the anal orifice.

Operation (August 9, 1948).—Hæmorrhoidectomy and excision of the polyp.

Histological examination of the polyp showed the structure of a carcinoid tumour.

Follow-up (February 6, 1950).—Patient looks well. *Abdomen*: Liver not enlarged. No abnormality felt. *P.R.* No induration. No sign of recurrence. *Proctoscopy*: No abnormality seen.

Pathological aspects.—It is usually necessary to perform a biopsy with microscopic examination in order to substantiate the diagnosis. Even with microscopy a number of pathologists have mistaken it for carcinoma.

The type cell: The present view is that the tumour arises from the argentaffine cells of the gastro-intestinal tract which were described by Kultschitzky in 1897 as specialized epithelial cells with a characteristic structure. In 1905 Schmidt called attention to their yellow colour and thought that they were part of the chromaffine system. In 1914 Gosset and Masson noticed that certain granules in the cell cytoplasm reduced silver compounds, producing brown or black particles, and called them argentaffine cells. These cells are commonest in the appendix and terminal ileum; less frequent in the large bowel and upper part of the small bowel, and comparatively rare in the rectum and stomach. They are concentrated at the bases of the crypts of Lieberkühn, and cases are described where a carcinoid tumour was demonstrated histologically to be arising from this region. The stroma of the tumour is composed of dense connective tissue and smooth muscle fibres with hyaline degeneration in places. The stroma is infiltrated by lymphocytes, plasma cells and polymorphs.

Malignancy

In reaching a decision concerning malignancy it is essential to consider the behaviour of the tumour, which is capable of giving rise to widespread metastases. Thus, Ritchie and Stafford (1944) reviewed a series of 332 cases and found 126 (37·9%) with metastases. Miller and Herrmann collected 68 cases with metastasizing carcinoid of the gastro-intestinal tract; 50 cases of small bowel; 14 cases of appendix; 3 cases of colon, and 1 of stomach. In Raiford's series of 29 cases, metastases were found in 20·7%. Pearson and Fitzgerald found metastases in 12·5% of a series of 32 cases of carcinoid tumours of the rectum. It may be that the incidence of metastases increases with the age of the tumour; for example, it is low in the appendix cases, for appendicectomy is usually carried out early. Burckhardt claimed that, although cell proliferation is slow, the formation of metastases is only a matter of time, dissemination occurring mainly by the blood stream and occasionally by the lymphatics. As the tumour gets larger, its tendency to metastasize becomes greater; and Gáspár stated that even the smallest nests of cells possess the ability to infiltrate the muscle layers.

The distribution of metastases resembles that seen in adenocarcinoma of the bowel; the liver and regional lymph nodes are most often involved. Metastases are described in other organs including the kidneys, suprarenals, spleen, brain, lungs, bone, subcutaneous tissues and mediastinal lymph nodes.

In addition there is other evidence of the malignant properties of this tumour. Cruickshank and Cunningham drew attention to the variability in the number of mitotic figures in the cells of different tumours; in some they are numerous indicating rapid growth. They also found evidence of cellular infiltration into, and through, the muscularis coat on frequent occasions, and even in small tumours lymphatic and vascular embolism was demonstrated. These authors are surprised that extensive metastases are not more frequent in addition to those in lymph nodes and liver. There is also a lesson in Morgan's case where a carcinoma of the cæcum had spread into the pericolic fat but no metastases had occurred, whereas a carcinoid was present in the same specimen situated 5 ft. from the ileocæcal valve with invasion of the muscle coat and metastases in 3 mesenteric lymph nodes.

A tumour with these properties must be regarded as malignant, but it progresses slowly, and it is agreed that the degree of malignancy is less than in adenocarcinoma. As the tumour enlarges its cells will eventually transgress their barriers with infiltration of neighbouring structures and metastases in distant organs may occur.

Treatment of Rectal Carcinoid

It should be remembered that the tumour possesses a low degree of malignancy, that after local excision there has been no recurrence in a number of cases after many years of observation, and that local infiltration is a danger sign. It is possible therefore to formulate the following programme of treatment.

When a carcinoid tumour has been excised in the belief that it was an adenomatous polyp, subsequent histological examination proving the diagnosis, the patient should be kept under observation in order to detect any recurrence. When a small, non-infiltrating carcinoid is found and confirmed by biopsy, a wide local excision is performed and the patient kept under observation. A radical operation is performed when a large carcinoid with infiltrating properties is present, or an annular constricting carcinoid.

If a recurrent carcinoid appears a radical operation should be carried out.

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[*March* 8, 1950]

Extensive Crohn's Disease.—A. DICKSON WRIGHT, M.S.

The patient, a man aged 31, has been more or less an invalid for the last ten years. In 1939, he was operated on for suspected appendicitis, but although a condition of well-established Crohn's disease was found, nothing was done except appendicectomy. Following this he was never well and eventually became obstructed in 1942, when an ileo-transversostomy was done. Following this, fæcal fistulæ appeared in the wound and several direct attempts to close them during the next five years only made bad worse, and when first seen in late 1948, his state was pitiable. Emaciated and anæmic, he was pouring pus and fæces from numerous fistulæ in the abdominal wounds, at the root of the scrotum and from a ring of anal fistulæ. Defæcation was extremely painful and the rectum was extensively ulcerated and stenosed. As a crowning humiliation he was passing flatus and fæces with his urine (Fig. 1). A skiagram at this time revealed a rabbit warren of tracks linking up small intestine, ileo-transversostomy, bladder and rectum (Fig. 2).

The skin of the abdominal wall which was excoriated and ulcerated, was rehabilitated by the ventral position for fourteen days and the abdomen was opened by a transverse incision to the left of the mid-line; the ileo-transversostomy was found to be reached and passed by the disease. The ileum was divided 12 in. above obvious disease and the distal end infolded and the proximal implanted into the transverse colon close to the splenic flexure. The sigmoid colon was divided near to its junction with the rectum, the distal end infolded and the proximal end brought out as a terminal colostomy. In anticipation of fluid fæces for a time, this colostomy was made of the penile type by the use of Thiersch grafts.

Following this, his miseries greatly diminished, the pneumaturia stopped and one fistula remained open on the abdomen discharging a small amount of pus and no fæces. The rectal fistulæ and ulcerated stricture were still present, but defæcation agonies were no longer necessary.

Ten months later with a much improved patient, further operation was carried out and all the diseased ileum together with more than the right half of the colon was resected. In doing this the fistulous tracts to the rectum were cut across and were stuffed with omentum. The specimen was typical Crohn's disease. The patient insisted on a general anæsthetic for this operation as his morale was getting a little low, and as a result of this developed a lung

abscess due to *Bacillus coli* in the left upper lobe (Fig. 3A). The lobe quickly melted away and had to be removed owing to fever and sputum (Fig. 3B). He recovered well from this third operation and is now strong with his weight 2 st. above that when first seen and with

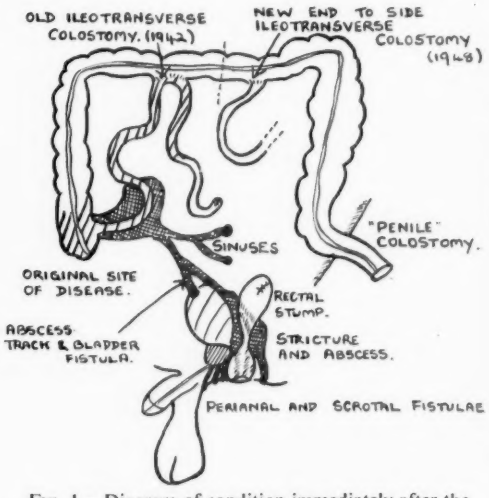
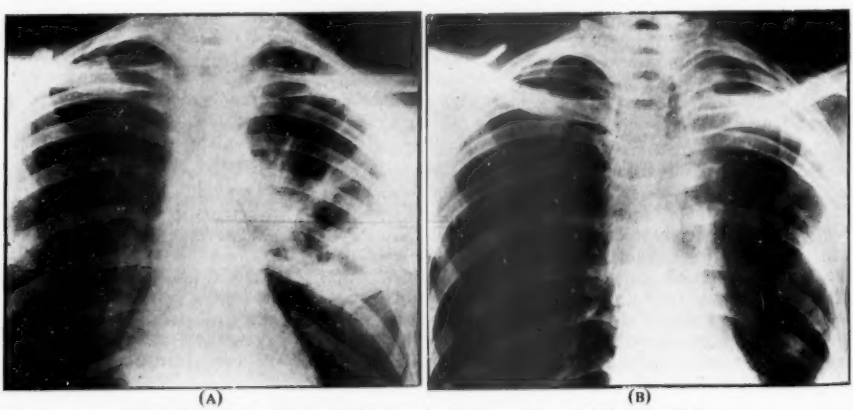


FIG. 1.—Diagram of condition immediately after the exclusion anastomosis.



FIG. 2.—Skiagram obtained by injecting anal fistulæ showing extensive fistulæ and abscess cavities.



(A) (B)

FIG. 3A and B.—X-rays before and after resection of left upper lobe.

no anæmia. It is proposed to resect the rectal mucosa at an early date and if the fistulæ heal and the sphincters are not destroyed, the possibility of bringing his colostomy through the anal sphincters is entertained.

The real object in showing the case is to illustrate the serious consequences and misery entailed by failing to do an ileo-transversostomy *with exclusion of the diseased intestine* when the condition is first discovered.

Reconstructive Abdomino-Perineal Excision of the Rectum [*Four Cases: Summary*].—S. O. AYLETT, M.B.E., F.R.C.S.

If, in selected cases of carcinoma of the rectum, the surgeon is to consider a sphincter-preserving operation he is not absolved from the responsibility of carrying out the widest possible excision compatible with continence. For this reason I consider anterior resections and pull-through operations to have no part in the treatment of this disease, as the areas excised are too limited.

Reconstructive abdomino-perineal excision has been criticized on the grounds that intractable fistulæ result. In presenting these 4 cases I wish to show that although perineal fistulæ may form, their closure is not long delayed, provided the anal stump and the adjacent anastomosed colon are kept emptied by twice daily washouts. To the patients little inconvenience is caused by the temporary fistulæ.

It seems therefore that the only objection to this operation is theoretical. As it approximates more closely to Miles's classic procedure than other limited resections, I feel that it should be more widely adopted. Babcock's operation is similar in extent but, in my experience, does not result in the full continence that is a feature of the cases upon which I have performed this operation.

Carcinoma of Rectum Invading Base of Bladder. Recto-cysto-prostatectomy and Transplantation of Both Ureters.—FRANK FORTY, F.R.C.S., and R. TREVOR JONES, F.R.C.S.

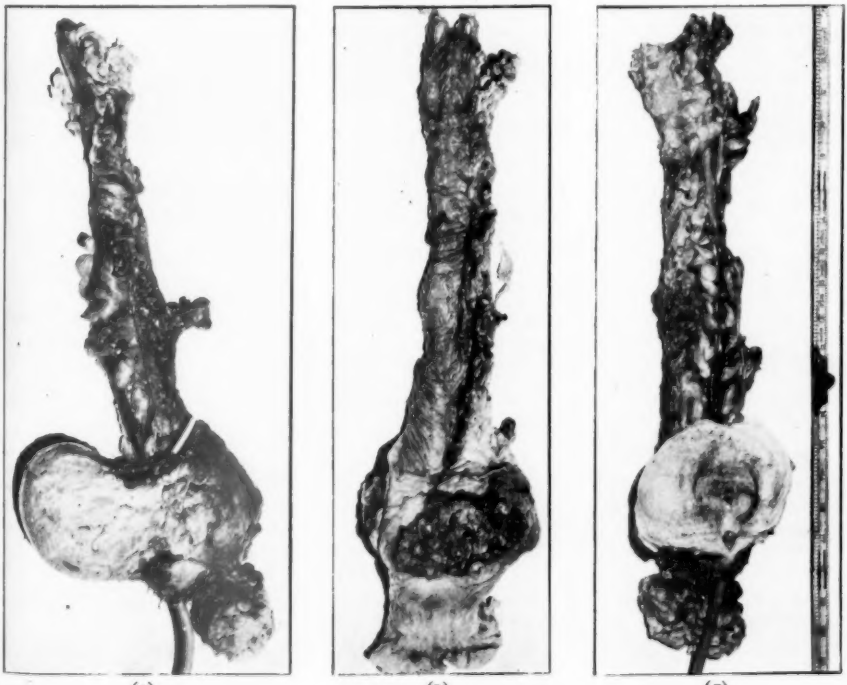
C. L., male, aged 61. Admitted to Edgware General Hospital October 23, 1949.

History.—Diarrhœa and occasional bleeding from rectum for one year. No urinary symptoms.

Examination.—Abdomen: Some gas distension. *Per rectum:* Nodular tumour filling ampulla and firmly fixed anteriorly. Cystoscopy: Marked bullous œdema of floor of bladder. Intravenous pyelography: Normal anatomy and function of both kidneys and ureters.

Operation (November 10, 1949). — Anæsthesia: Pentothal-spinal-gas-oxygen-ether — Dr. J. H. Attwood. Abdominal exploration: Growth fixed to peritoneum of recto-vesical pouch. Bladder indurated and inseparable from growth. Loop of sigmoid colon attached to the tumour mass. No enlarged glands or liver metastases. Procedure: Synchronous abdomino-perineal excision.

Per abdomen: The peritoneal incision on either side of the rectum, after skirting wide of the growth, was carried forwards over the top of the bladder as far as the pubis. Both ureters were divided close to the bladder. The rectum and bladder were freed *en masse* from the pelvic wall on all sides.



(A) (B) (C)

FIG. 1.—Operation specimen: (A) from the side: bladder distended; tubes mark membranous urethra and left ureter. (B) From the back: rectum opened posteriorly. (C) From the front: bladder opened anteriorly.

We are indebted to Miss M. H. Shaw for the photographs.

Perineal dissection: The incision was carried from the base of the coccyx, around the anus, as far forwards as the root of the scrotum. The levatores ani, both layers of the triangular ligament and the membranous urethra were divided. The prostate and the neck of the bladder were freed from the pubis, allowing the mass comprising rectum, bladder and prostate to be withdrawn through the perineum (Fig. 1).

Transplantation of ureters: Modified Coffey II technique. Ureters splinted with "Portex" plastic tubing introduced as far as the renal pelvis, and secured by a silk ligature tied around the lower end. Lower end of right ureter drawn $\frac{1}{2}$ in. into the cæcum and secured by a few stitches. Portex tube brought out through the stump of the amputated appendix and the abdominal wall in the right iliac fossa. Left ureter similarly implanted into the descending colon and Portex tube brought out through the left iliac end-colostomy (Fig. 2).

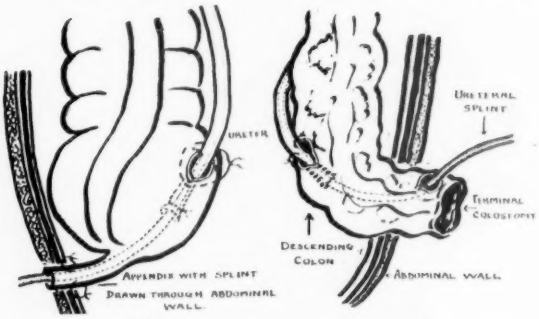


FIG. 2.—Diagrams showing method of implanting ureters, using indwelling splint of "Portex" plastic tubing. (A) Right ureter into cæcum. (B) Left ureter into descending colon.

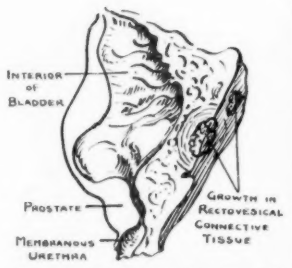


FIG. 3.—Sagittal section through bladder showing penetration of growth into recto-vesical tissues and the enveloping zone of chronic inflammatory fibrosis.

Progress.—Uneventful recovery after initial ileus had been overcome by carbachol and an enema on the sixth day. Ureteral tubes withdrawn on eighth and twentieth days respectively, followed by rapid healing of stab incision in abdominal wall. Intravenous pyelogram four months after operation shows moderate dilatation of renal pelvis and calyces on both sides and good excretory function.

Microscopical report (Dr. L. W. Proger).—Well-differentiated columnar-cell adenocarcinoma with extensive mucoid areas. The tumour is deeply infiltrating the rectal wall which is firmly adherent to the bladder. The bladder wall and intervening tissues show intense chronic inflammatory infiltration (Fig. 3).

COMMENT

Recto-cysto-prostatectomy is unlikely to be often performed for it is indicated only in the following circumstances:

(1) The growth in the rectum has invaded the base of the bladder.
(2) The ureters are not invaded.
(3) Local, peritoneal and lymphatic spread are not beyond the limits normally precluding an abdomino-perineal excision of the rectum.
(4) The liver is free from metastases.
(5) The patient is young enough and fit enough to withstand a formidable operation.
(6) The patient understands the nature of his subsequent disability and is capable of managing a wet colostomy.

Under these conditions recto-cysto-prostatectomy provides a worth-while extension of the scope of radical surgery in advanced carcinoma of the rectum.

Chronic Ulcerative Colitis with Pseudo-polyposis Terminating in Diffuse Colloid Carcinoma of the Colon.—W. B. GABRIEL, M.S., F.R.C.S.

CASE I.—E. S., male aged 42 when first seen as an out-patient at St. Mark's Hospital, 13.3.33.

History.—He complained of rectal bleeding and occasional incontinence; he had previously been treated elsewhere for colitis.

Examination.—He presented a granular proctitis which sigmoidoscopy showed was limited to the lower 6 inches of the bowel.

Course.—Medical treatment was carried on with variable success: periods of quiescence varied with bouts of exacerbation and ten years later (1943) he was keeping well and sigmoidoscopy showed very little amiss—only a slight suggestion of granularity. In 1945 his colitis became more active with passage of loose offensive stools; this settled down on sulphaguanidine.

In May 1947 he suddenly began to go downhill, with loss of weight and some abdominal pain before the bowels moved. When admitted (3.6.47) there was an alarming change in his appearance; his abdomen was slightly distended and free fluid could be demonstrated. A barium enema showed areas of chronic stenosis involving the pelvic colon and distal part of the transverse colon: in the pelvic colon the view suggested the presence of granulomas and this was confirmed by sigmoidoscopy which showed heaped-up granulations. A biopsy was done and sections showed inflammatory polyps but no sign of malignancy. On June 10, 1947, a paracentesis of the abdomen was done and 10 pints of fluid removed.

Operation (12.6.47).—The abdomen was explored through a right paramedian incision and free fluid removed by sucker. The great omentum was found to be about an inch thick and infiltrated solidly with carcinoma; the parietal peritoneum was also studded with fine nodules. The site of the primary growth could not be determined with certainty. A wedge was taken from the omentum for section and the abdomen closed.

Subsequent course.—The patient went steadily downhill and died on 20.6.47. His age at this time was 56 years.

Post-mortem.—The post-mortem examination showed an advanced stage of ulcerative colitis affecting the whole colon and also a stricture in the transverse colon. Sections of this stricture showed a very anaplastic type of colloid carcinoma spreading into the muscle and pericolic fat and causing metastases in the mesenteric lymph glands. The omentum was bound down to the growth by dense adhesions and was permeated throughout by carcinomatous growth (Dr. Cuthbert Dukes).

CASE II.—Mrs. L. P., aged 40 when first seen in the O.P. Department at St. Mark's Hospital, 6.6.39.

History.—She gave a history of diarrhœa with passage of blood and mucus for two years.

Examination.—She was a thin pale woman and sigmoidoscopy showed a severe ulcerative colitis with a thickened inelastic wall, small areas of polypoid mucosa and much pus coming down from above.

Operation (8.6.39).—Appendicostomy performed and opened a week later by cutting it across with a cautery.

Subsequent course.—Daily washouts with saline and bicarbonate lotion were then begun, together with olive oil instillations at bedtime, and on this routine she improved quickly and put on weight. By October 1939 the rectal mucosa appeared pale and smooth.

In 1941 she developed a chronic cough and was X-rayed with indefinite findings, but in 1943 and 1945 definite X-ray evidence of pulmonary tuberculosis was obtained, although the sputum was negative. During this time her colitis remained fairly quiescent, although in 1940 and again in 1941, 1943, and 1946, granulomatous polypi were removed from the rectum and were pronounced to be benign.

In May 1945 a barium enema examination showed multiple filling defects in the descending iliac and pelvic colon, which it was thought might represent hyperplastic tuberculous nodules rather than simple adenomas or granulomas.

In 1947 she began to go downhill and lost weight. Her abdomen had a "doughy" feel, with an indefinite mass palpable in the left iliac fossa and it was thought that these findings were explainable on a basis of tuberculous peritonitis. In addition she had a pocket in the posterior wall of the anal canal, which was probably evidence of a chronic tuberculous ulceration.

In October 1949 she was seen again as an out-patient; she had a pronounced moist cough and had wasted greatly. On January 9, 1950, she was sent up as an emergency with subacute intestinal obstruction. Her abdomen was distended, with a palpable mass (? fæcal), in the left iliac fossa. Rectal examination revealed a tight rectal stricture through which a finger could not be passed.

Operation (12.1.50).—Right paramedian incision. Free fluid was present. The left half of the colon was greatly thickened: the pelvic colon was adherent in the left iliac fossa and felt curiously hard and greatly thickened. Pin-head nodules were found in relation to the terminal ileum and cæcum and were thought to be suggestive of old tuberculous peritonitis. A terminal ileostomy was established and the distal end closed flush with the cæcal wall.

Subsequent course.—On the day following operation her condition was quite satisfactory, but on the second post-operative day she had an epileptiform fit with frothing at the mouth; this proceeded to coma and she died a few hours later. Her age now was 50.

Post-mortem findings (Dr. Cuthbert Dukes):

Abdomen: A large quantity of clear yellow fluid. Slight adhesions in coils of small intestine near ileostomy. Mesentery of small intestine thick and fibrous and covered with tubercles. Large mass in pelvis surrounding rectum. Hæmorrhoidal and aortic glands much enlarged. Wall of rectum and colon massively thickened. Polypoid tumours in distal end of pelvic colon but no visible tumour in rectum which showed a dense fibrous stricture. Liver pale and shrunken. No metastases present. Spleen much enlarged and very soft. Left suprarenal showed hæmorrhage.

Thorax: Effusion in both pleural cavities and into pericardium. Heart normal. Right lung contained old tuberculous lesion at apex. Dense adhesions to chest wall.

Brain: Some œdema and congestion. No sign of hæmorrhage or thrombosis.

Cause of death: Generalized œdema, especially with abdominal effusion, associated with chronic ulcerative colitis on which colloid carcinoma had supervened leading to carcinomatosis peritonei.

Microscopic structure of tissues removed at autopsy—

Rectal stricture: Colloid carcinoma spreading diffusely in the perirectal tissues.

Hæmorrhoidal glands: Several metastases present.

Aortic glands: No metastases found.

Right lung: Active tuberculous lesion.

Peritoneal nodules on small intestine, &c.: Secondary deposits of carcinoma.

COMMENT

In both of these cases expectant treatment was carried on for too long.

In the first case an ileostomy and total colectomy should have been done in November 1945, when the barium enema films showed a chronic procto-colitis reaching the ulcerative stage. A review of the clinical notes indicates that malignant change and its development to the inoperable stage took place during the last six months of this patient's life and the rapid extension of the growth is well explained by the microscopical findings that it was of the high-grade anaplastic type.

In the second case my attitude towards the bowel condition and its treatment was biased by the fact that the patient was proved to have pulmonary tuberculosis. Later events showed that she should have had an ileostomy and a total colectomy at least five years before she reached the terminal stage in 1950.

These cases show that the development of pseudo-polyposis should constitute a grave warning of worse to come and provide a certain indication that ileostomy and total colectomy have become necessary. R. A. Scarborough and R. R. Klein (1948, *Amer. J. Surg.*, **76,** 723) mention a series of 15 patients with pseudo-polyposis secondary to chronic ulcerative colitis, and 4 of these patients had a carcinoma, which, in 3 cases, proved to be inoperable.

The only real hope for these patients with advanced fibrosing ulcerative colitis is for radical surgery (colectomy) to be undertaken *before* the onset of malignant change.

Squamous-cell Carcinoma Arising in Post-rectal Dermoid Cyst.—CUTHBERT DUKES, O.B.E., M.D., F.R.C.S.

[Dr. Cuthbert Dukes showed an operation specimen illustrating the development of squamous-cell carcinoma in a post-rectal dermoid cyst.]

History.—The patient, Mrs. A. S., now aged 41, first attended St. Mark's Hospital in 1935 complaining of the discharge of pus from the rectum: first noticed when she was only 6 months old.

On examination.—A rough granular area was present on the mucous membrane of the posterolateral wall of the rectum. Biopsy from this region showed only normal mucous membrane and inflammatory cells.

From 1935 to 1949 the patient attended St. Mark's Hospital frequently, and also other hospitals. The condition was generally regarded as a chronic abscess, but in May 1935 Mr. Naunton Morgan had already written in the patient's notes: "This is probably a suppurating perirectal congenital cyst."

Biopsy.—In April 1949 a small papilloma was noticed situated on a tender swelling in the left posterolateral quadrant of the upper third of the rectum. Biopsy from this region now showed squamous epithelium undergoing proliferation and this was assumed to have been derived from the fistulous opening of the cyst.

Operation.—In July 1949 the opening appeared to be larger and further biopsy now revealed squamous-cell carcinoma. For this reason a synchronized combined excision of the rectum was carried out by Mr. Naunton Morgan and Mr. Lloyd-Davies. The patient made an uneventful recovery from the operation and is now in good health.

Pathology.—Examination of the operation specimen showed a small ulcerated area surrounding the fistulous opening in the left posterolateral quadrant of the upper third of the rectum (Fig. 1). This communicated with a cystic tumour situated between the rectum and sacrum, measuring about 3 in. in diameter, surrounded by a fibrous capsule and occupied by rather soft greyish-white material (Fig. 2). Tissue was removed for section from the tumour, from the fistula and from the ulcer in the rectum and in each case the sections showed squamous-cell carcinoma only (Fig. 3). The growth was of the keratinizing type. No other neoplastic tissue was found. Metastases of squamous-cell carcinoma were present in two of the hæmorrhoidal lymphatic glands.

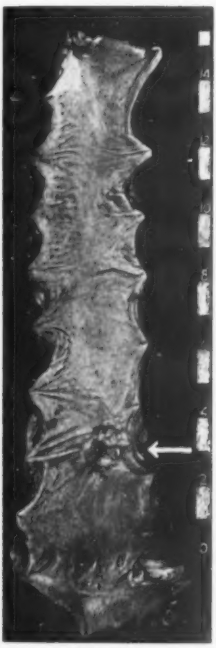


FIG. 1



FIG. 2

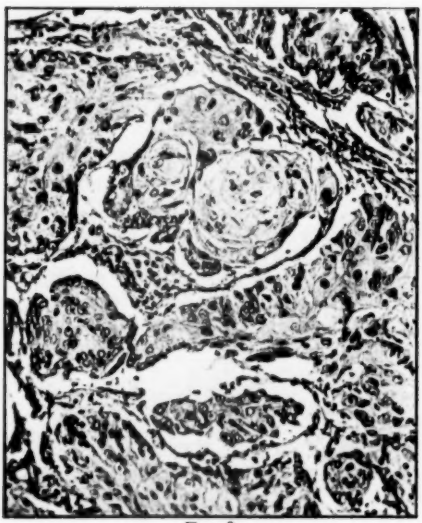


FIG. 3

FIG. 1.—Surface view of operation specimen showing ulcer round fistulous opening in posterolateral quadrant of rectum.

FIG. 2.—Slice through operation specimen showing tumour which was situated between the rectum and sacrum.

FIG. 3.—Section from tumour showing squamous-cell carcinoma. × 400.

COMMENT

Most pre-sacral and coccygeal teratomas are benign and cystic in character but they may become malignant, some even in infancy. In my experience when malignancy occurs in infancy the tumour has the histology of an intracystic papillary adenocarcinoma, but when malignancy does not supervene till later (as in this patient at the age of 40) then the carcinoma is of a squamous-cell type. Another point of interest is that when carcinoma develops it is of the same histological pattern throughout, that is, either pure adenocarcinoma or pure squamous-cell carcinoma, as if derived from one only of the epithelial components of the teratoma.

Two Cases of Crohn's Disease Treated by Right Hemicolectomy.—R. W. RAVEN, O.B.E., F.R.C.S.

The case histories of these two patients illustrate the marked difference in the symptomatology of Crohn's disease even though the morbid anatomy of the bowel may be similar. The symptomatology described here is maximal and minimal in severity.

CASE I.—Female, aged 55, complained of abdominal pain for three months.

History.—The pain was griping in nature across the centre of the abdomen, lasting ten minutes, about once a day. Relieved by food; remissions of one or more days. Bowels open regularly. Nausea and sometimes retching. Weight loss of 9 lb.

Examination.—Thin. Abdomen: No tenderness or swelling. No distension. Liver, kidneys and spleen not palpable. P.R.—no abnormality.

Radiological examination of colon.—The cæcum was fixed on palpation. There was a rounded filling defect in the region of the ileocæcal valve, which appeared to be a neoplasm. I thought it might be due to cæcal residue, but on repeated examination it was unchanged.

Operation (September 28, 1949).—Right hemicolectomy with ileotransverse colon anastomosis (end-to-side).

Specimen.—Wall of terminal ileum diffusely thickened. Process extending beyond ileocæcal junction into wall of cæcum for a short distance. Stenosis of terminal ileum. Some mucosal ulceration.

Histology.—Regional ileitis with fibrosis.

Follow-up.—Patient is well. Gained 11 lb. weight. Bowels normal. No abdominal pain.

CASE II.—Female, aged 30. Complained of chronic ill-health.

History.—Patient was well till 1941, when she suddenly commenced to have diarrhœa with loss of weight. This occurred in attacks, 5 bowel actions a day, none at night. Severe abdominal pain. In 1944 appendicectomy; diarrhœa disappeared and she gained 1½ st. in weight. Nine months later weight loss and diarrhœa recurred. In 1947 she experienced severe abdominal pain with vomiting. Her symptoms continued up to the present with severe loss of weight, irregularity of the bowels—sometimes diarrhœa, at other times constipation—occasional blood in stools. Physeptone required for the pain.

Examination.—Patient very thin and pale. Abdomen: Marked tenderness in right lower quadrant, less in the left. No swelling. Liver, kidneys and spleen not palpable. P.R.—no abnormality.

X-ray examination.—At twenty-four hours barium was still present in the last 2 in. of the terminal ileum; filling showed a rugged cæcum and it was very tender and spastic.

A diagnosis of Crohn's disease was made and arrangements completed for patient to enter hospital for operation.

During the waiting period she developed complete intestinal obstruction of the small bowel. This was relieved by intubation, intravenous fluids, &c.

Operation (September 27, 1949).—Right hemicolectomy with ileotransverse colon anastomosis (end-to-side).

Specimen.—Specimen comprises colon, some 16 cm. of which is normal. The serous surface of the remainder of the bowel is inflamed and sharply kinked in two places by firm adhesions. The length of the bowel thus affected is some 30 cm. Beyond this point there are 14 cm. of normal bowel. On opening the bowel the wall of the affected part is greatly thickened. The mucous membrane is smooth and œdematous.

Histology.—Regional ileitis.

Follow-up (February 17, 1950).—Patient is well. Gained 2 st. 3 lb. Bowels—some looseness. No abdominal pain.

Chronic Ulcerative Colitis—Two Specimens.—RUPERT CORBETT, M.Chir., F.R.C.S.

(1) *Ulcerative colitis, associated with pyoderma of the legs.*

A male medical student, aged 21.

History.—Has suffered from pyoderma—especially of the right leg—for the past four years. In an attempt to heal the ulceration in the leg, four skin-grafts had been carried out and on one occasion, associated with a right lumbar gangliectomy. There was no improvement.

The colitis varied from time to time but was not severe. The patient feared the loss of his limb and was, therefore, prepared to consider more drastic treatment for the colitis. I advised and carried out a subtotal colectomy after the method of Devine. After removal of the colon, the ulceration of the leg completely disappeared and it has remained healed. He is now passing two motions a day *per rectum*, having lost the greater part of his colon which showed pseudopolyposis.

(2) *Colon and portion of ileum showing involvement in chronic ulcerative colitis.*

A youth, aged 20.

History.—Four years ago he had a fulminating attack of ulcerative colitis. An emergency ileostomy was carried out and he made a great improvement. At this time division of the ileum was carried out 9 in. from the ileocæcal valve as the disease had already spread into the terminal ileum. At the level of the division it was thought to be clear of further trouble; this, however, was not the case because, four years later, a subtotal colectomy was carried out. It was then noticed that a further portion of small intestine had to be removed before the normal segment was reached which was applied to the rectosigmoid stump. This illustrates the fact that extension of the disease can take place well into the small intestine.

Regional Colitis.—HENRY R. THOMPSON, F.R.C.S.

R. B., female, married, aged 28.

Past history.—1947 miscarriage. 1949 miscarriage. No history of abdominal pain or bowel irregularity.

18.9.49: Woken up at 8 a.m. with sudden severe abdominal pain. After taking a dose of Epsom salts commenced severe diarrhœa with passage of blood and repeated vomiting. Examination suggested a pelvic peritonitis, due to perforated appendix.

Operation.—Grid-iron incision. Appendix found normal. Mid-line upper abdominal incision. Transverse colon found to be œdematous and discoloured. As the diagnosis was uncertain the abdomen was closed.

Four days later: A recurrence of severe abdominal pains with blood-stained stools. This settled, but nine days after the operation colicky abdominal pain occurred with diarrhœa and the passage of very offensive blood-stained liquid stools. Provisional diagnosis of intussusception and intestinal obstruction was made.

27.9.49: *Operation*—Laparotomy. The whole of the small intestine was dilated. Visceral peritoneum was injected. There was an area in the transverse colon 3 in. long close to the hepatic flexure which was red, constricted and thickened with small shotty glands in the adjacent mesentery. The abdomen was again closed. Post-operatively the diarrhœa and passage of blood *per rectum* continued, and the hæmoglobin fell to 48%. She continued to have mild attacks of colic. Sigmoidoscopy showed the rectum and lower colon to be normal. X-ray of chest was negative for pulmonary tuberculosis.

10.11.49: Barium enema showed a constriction in the proximal part of the transverse colon extending for 2 in. to 3 in. The anæmia was corrected by blood transfusions.

21.11.49: *Operation* (nine weeks after onset of symptoms).—Right paramedian incision. Inflammatory thickening localized to the right part of the transverse colon 2 in. to 3 in. in length. Right hemicolectomy performed. Side to side anti-peristaltic ileo-transverse colostomy. Post-operative recovery uneventful. Discharged from hospital December 10, 1949, symptomless. Bowels opening twice daily, stool formed and normal.



FIG. 1.—Appearance of peritoneal surface.



FIG. 2.—Appearance of mucosal surface.

Specimen.—This consisted of the cæcum, ascending colon and transverse colon. The cæcum and ascending colon were enormously dilated but in the region of the transverse colon the bowel was contracted and thickened over a distance of 5 in. No tumour or obvious ulceration was present in this region but the mucosal surface showed hæmorrhages and fissures and the bowel wall had lost its normal elasticity (*see* Figs. 1 and 2).

Microscopic structure.—Sections show dense infiltration of submucosa with inflammatory cells chiefly lymphocytes together with œdema and fragmentation of the muscle coat. The lymphatic glands show reactive hyperplasia only.

COMMENT

The gross characters of the lesion resemble ileitis and the histology is consistent with this though there is no giant-cell formation in the lymph follicles. In some ways the naked-eye character of the specimen is more typical than the microscopic picture, but this may be due to the fact that the lesion is at an early stage of development.

Cyst of Anal Intermuscular Gland.—HENRY R. THOMPSON, F.R.C.S.

J. F. D., male, aged 34.

Eighteen months' history of swelling at anus, slow increase in size, especially over the last few months. Soreness on sitting down.

24.11.49: Excision of semi-pedunculated swelling which consisted of a cyst with a prolongation extending up between the subcutaneous and superficial external sphincter. No communication of the cyst with the anal canal could be demonstrated.

Post-operatively wound healed and has remained healed with no suggestion of a fistula forming.

Specimen consisted of a pedunculated tumour covered by skin and attached by a funnel-shaped stalk to the anal canal. Dissection showed the interior of the tumour to be occupied by a cyst lined by a smooth glistening capsule which was prolonged up into the stalk of the tumour (*see* Figs. 1 and 2).

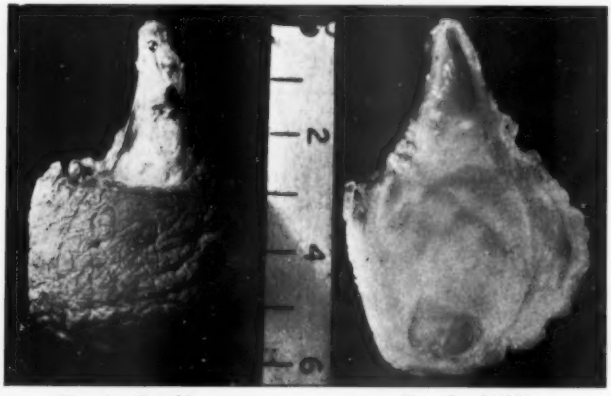


FIG. 1.—Outside.

FIG. 2.—Inside.

Histology (Dr. Cuthbert Dukes).—The "tumour" is really nothing more than a cyst with a funnel-shaped extension upwards in the pedicle. The cyst is lined with transitional epithelium similar to that normally present in the intramuscular glands of the anal canal. Surrounding this is the capsule of the cyst which is composed of connective tissue containing a few collections of inflammatory cells, including some giant cells. The outer surface is covered with a thick layer of stratified squamous epithelium producing large quantities of keratin. There is a striking difference between the thin layer of transitional epithelium lining the cyst and the thick layer of squamous epithelium on the outside. The most likely explanation is that the cyst is derived from an obstructed intramuscular gland.

Three New Families of Intestinal Polyposis.—TOM ROWNTREE, F.R.C.S.

The first patient who stimulated my interest in this subject was Florence A. She had recently been found to have polyposis and a colectomy had been performed. Her family was investigated; her two brothers were found to be suffering from the disease. Her father had died from cancer of the rectum arising in polyposis. She stated that her aunt, Mrs. V.. had died at St. Mark's from a similar condition. Hitherto there had been no knowledge of the connexion between the V. and the A. families, and we have now learned the importance of recording the maiden name of all female cancer patients.

Further enquiries brought to light a few more relatives who were persuaded to attend for examination. Every clue was followed, and, after correspondence with Somerset House and with numerous hospitals, the family tree shown in Fig. 1 was constructed.

It is a huge family and many of the unaffected members have had to be grouped in a single symbol for the sake of space. The first traced member of the family was William A. who died from cancer of the rectum at the age of 67. He had 10 children, 5 of whom died of cancer of the rectum or colon. A sixth, Mrs. D., died of intestinal obstruction, but no post-mortem was performed. It is likely that she had a carcinoma because, of her 12 children, two died of carcinoma of the large intestine superimposed on polyposis, and a third had secondaries in the liver, there being no record of the site of a primary growth.

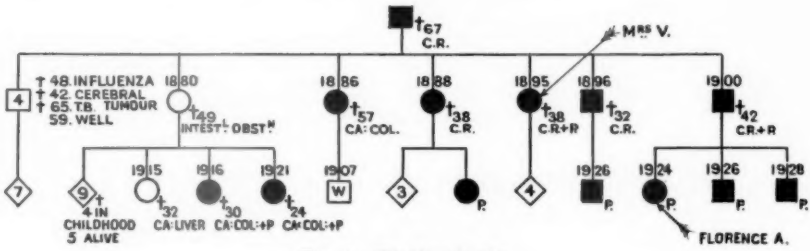


FIG. 1.—The first family.

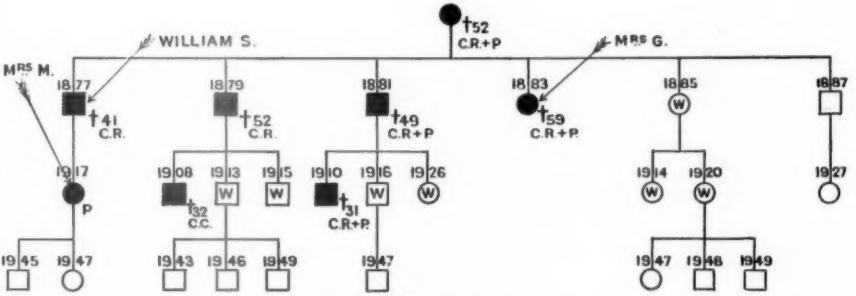


FIG. 2.—The second family.

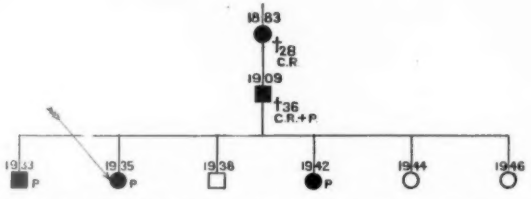


FIG. 3.—The third family. The arrow points to Margaret.

In each family tree the following symbols are used:

□ Male, unaffected	■ Male, affected	(W)	means "examined and found well".
○ Female, unaffected	● Female, affected	(7)	the number of persons represented.
◇ Both sexes		†	with a numeral: age at death.

The dates above each symbol are the dates of birth.

C.R.: proved carcinoma of rectum. Ca Liver: Cancer of Liver.
P.: proved polyposis. Ca Col., C.C.: Cancer of Colon.

Every case of polyposis or carcinoma indicated in the charts has been proved either from the death certificate, or from hospital notes or on examination by me.

The second family (Fig. 2) has had 3 members treated at St. Mark's. Mrs. G. had an inoperable carcinoma of the colon, and it was from her that most of the information was originally obtained. Her mother, Sarah S., died in the London Hospital from cancer of the rectum and polyposis at the age of 52 in 1904. I have been unable to trace further back than this. Of her 6 children, 2, namely Mrs. G. and William S., died after treatment at St. Mark's, and 2 died at other hospitals, all from cancer of the large intestine. There are two members of this generation still alive and well to-day. The condition is well represented in the third generation ; two members are already dead, while a third, Mrs. M., has recently undergone colectomy, when the specimen shown in Fig. 4 was obtained.

The third family is at present smaller than the other two, but I am now engaged upon tracing it further back (Fig. 3). Mrs. C. died of cancer of the rectum at the age of 28 and her only son died from the same disease at the age of 36. He begat 6 children, 3 of whom have already had symptoms and have been found to be suffering from polyposis while the other 3 have not yet been examined, on account of their youth. Margaret has undergone an operation at

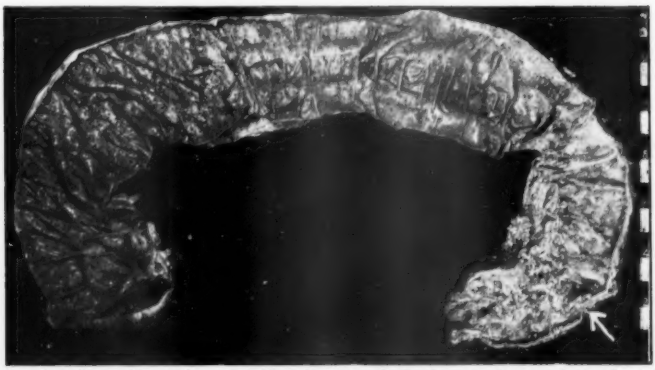


FIG. 4.—The colon from Mrs. M., aged 33, who already had a carcinoma (arrow) at the time of operation in February 1950.

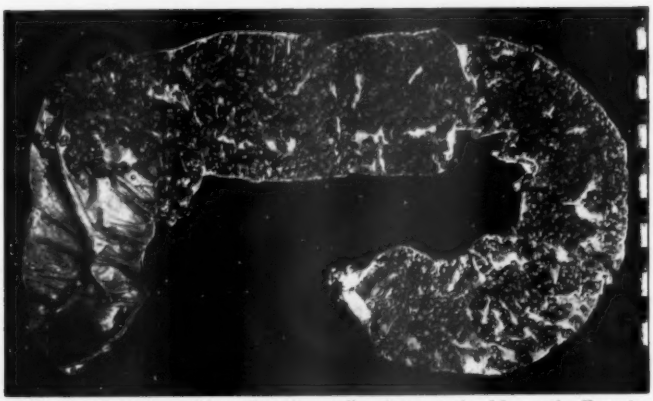


FIG. 5.—Margaret's colon. Note the abrupt line between healthy and affected colon.

which the specimen, Fig. 5, was obtained. The specimen is interesting in that it shows an abrupt change from healthy to affected bowel at the hepatic angle. This phenomenon is unexplained.

As a general rule, death occurs from cancer at an ever-decreasing age as each generation succeeds the other. It is likely therefore that, in a given family, the disease untreated will die out. Treatment of the individual prolongs his chances of begetting children doomed to polyposis. The construction of the family tree helps to determine for us the degree of dominance of the disease in that family, and so to advise more accurately upon the wisdom of avoiding further reproduction.

CORRIGENDUM

Clinical Section

(*March* 10, 1950)

Endarteriectomy in the Treatment of Chronic Endarteritis Obliterans of the Limbs and Abdominal Aorta by HENRY REBOUL, M.D., *Paris*, and PIERRE LAUBRY, M.D., *Paris*.

(*Proceedings*, **43**, 547, July 1950.)

P. 548, lines 7 and 8: "... to which 500 mg. of sodium nicotinate..." *should read* "... to which 50 mg. of sodium nicotinate...".

Section of Medicine

President—Sir ADOLPHE ABRAHAMS, O.B.E., M.A., M.D., F.R.C.P.

[*March* 28, 1950]

DISCUSSION ON THE PRESENT POSITION OF THE NEWER ANTIBIOTICS

Professor L. P. Garrod, *Dept. of Pathology, St. Bartholomew's Hospital.*

If we survey the whole field of antibiotic research as it exists to-day, we find that these substances are being recovered from an extraordinary variety of sources in the plant kingdom. Apart from fungi and bacteria, they have been extracted from algæ, lichens, toadstools, bananas, sweet potatoes, wallflowers and hops as well as a variety of other plants. On the other hand, few of these thousands of substances qualify as chemotherapeutic agents and these few are derived from three major sources. They are first the higher fungi (*Penicillia, Aspergilli*) and here it is of some interest that in spite of the examination of many species, of which at least one-third form antibiotics of some kind, none has been found to yield a substance other than penicillin which can approach it in therapeutic efficacy. Another important source is the more primitive group of fungi, *Actinomycetes*, and these have been found to yield three valuable antibiotics, streptomycin, aureomycin and chloromycetin. Thirdly there are the aerobic sporogenous *Bacilli*, from which many named antibiotics are derived, the best studied of which are the polymyxins, bacitracin, licheniformin and ayfivin. Although a few enthusiasts dispute this, majority opinion is against the parenteral use of these substances on account of their toxic effect on the kidney. If this conclusion be accepted, we are left only with the antibiotics derived from *Actinomycetes* to form the subject of this Discussion.

Since subsequent speakers are dealing with streptomycin, I shall confine my remarks henceforth to aureomycin and chloromycetin. (For discussion on streptomycin *see* p. 692). These antibiotics are formed by *Streptomyces aureofaciens* and *Streptomyces venezuelæ* respectively: the latter has also been synthesized, and in its synthetic form

is known as chloramphenicol. They both differ from their predecessors in that they are best administered by the mouth. It is not clear that absorption from the alimentary tract is complete, but it is sufficient, and adequate levels are maintained in the blood for several hours after a single dose. This is fortunate, since chloromycetin is too insoluble and aureomycin in its usual form too acid for solutions to be injected intramuscularly. Aureomycin can, if necessary, be injected intravenously in a large volume of solvent: it should never be injected intrathecally and this is, in any case, unnecessary since it reaches the cerebrospinal fluid via the blood. For the same reasons local application has been little practised, although aureomycin borate has been successfully used in treating conjunctivitis (Braley and Sanders, 1948).

No dangerous toxic effects have been noted from either drug. Both have a very bitter taste, and it is consequently difficult to get children to take them. Aureomycin tends to cause nausea and vomiting, and chloromycetin may produce anorexia and dryness of the mouth.

Whereas penicillin and streptomycin are both bactericidal, the former killing bacteria with moderate rapidity at its optimum concentration and the latter behaving like an ordinary germicide and killing more and more rapidly the higher the concentration employed, aureomycin and chloromycetin are both purely bacteriostatic. Theoretically this might be expected to mean that they should be administered for rather longer periods in conditions, such as urinary tract infections, in which any of the four may be indicated, according to the nature of the infection, and the circumstances are favourable for bactericidal effect.

These two new drugs have brought within the scope of effective chemotherapy a wide range of infections for which there was previously no dependable specific treatment. Perhaps the most important of these is typhus. Chloromycetin has an astonishing effect in scrub typhus (Lewthwaite, Chloromycetin in typhus and typhoid, *Proc. R. Soc. Med.*, 1950, **43**, Sect. Exper. Med., in Press), and it seems that all rickettsial infections respond to one or other of these two drugs, although their relative merits are not yet fully assessed (Woodward, 1949). It is equally remarkable that they have an action on a few viruses, notably those of lymphogranuloma venereum (Wright *et al.*, 1948), psittacosis, and primary atypical pneumonia (Kneeland *et al.*, 1949; Finland *et al.*, 1949*b*). Aureomycin has been chiefly used for these three diseases, and the usefulness of chloromycetin is less well established: to judge by the experimental results of Eaton (1950), chloromycetin would not be expected to be so useful in the last-named. According to Dawson and Simon (1949), aureomycin also has an effect on herpes zoster: this requires confirmation. Chloromycetin is apparently without influence on this condition. Chloromycetin is reported to be effective in trachoma. It must be understood that neither drug has the slightest action on many other important viruses, notably those of influenza and poliomyelitis.

Among bacterial infections also there are a number in which the two new drugs are superior to anything we have hitherto possessed. A general idea of this activity against the main bacterial species can be gained from Fig. 1 which shows the concentrations in μg per ml. inhibiting their growth as compared with that of penicillin. These are only approximate, since reported findings vary with the technique used, and in any case there is some strain variation. Two important general tendencies emerge from such a tabulation. It is clear that aureomycin has the greater activity against Gram-positive cocci, and this is borne out by clinical experience. To take two examples, it is a valuable standby in penicillin-resistant staphylococcal infections (Nichols and Needham, 1949), and it is effective in pneumococcal pneumonia (Finland *et al.*, 1949*a*): indeed it is effective in every kind of pneumonia including all common

bacterial forms and those due to viruses, and has thus been recommended as the safest drug to use when laboratory facilities are lacking (Herrell, 1949).

Chloromycetin, on the other hand, has an evidently superior activity against Gram-negative bacilli generally, and much the most important practical application of this is in the treatment of typhoid fever. Neither drug has a useful action on *Ps. pyocyanea*, and *Proteus* tends to be resistant, although rather less so. Both are active *in vitro* against the *Brucellas*, and this action has been confirmed clinically, the remarkably curative effect of aureomycin in undulant fever due to either *Br. melitensis* (Spink *et al.*, 1948) or *Br. abortus* (Braude *et al.*, 1949) having been shown by Spink

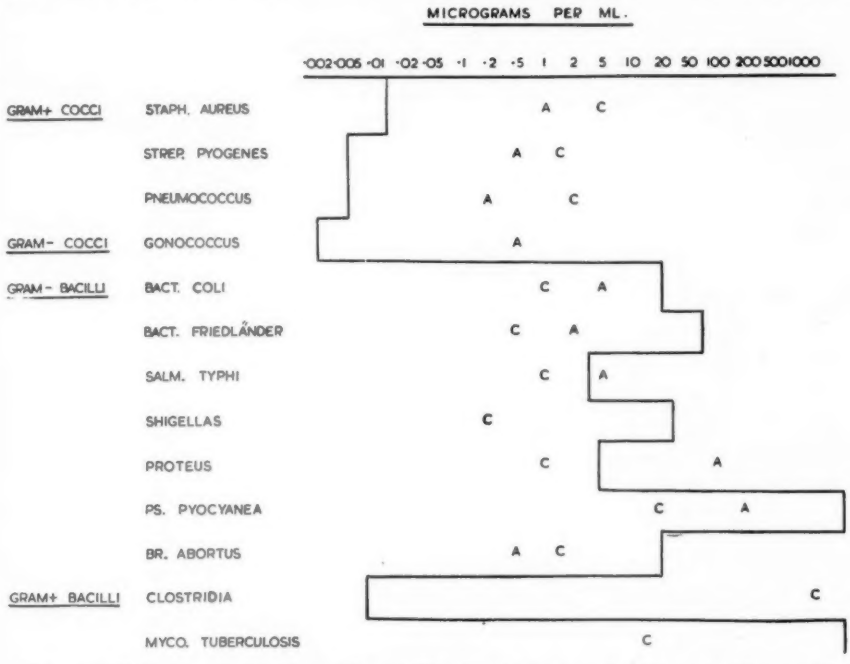


FIG. 1.—Minimum concentrations of penicillin (——), aureomycin (A) and chloromycetin (C) inhibiting growth.

and his colleagues and confirmed on a smaller scale in this country. Chloromycetin has also been used successfully but not yet on a sufficient scale to assess its relative merit.

Both drugs will cure gonorrhœa, and aureomycin has also an effect in non-specific urethritis (Willcox and Findlay, 1949) and in syphilis (O'Leary *et al.*, 1948, 1949), although its place in the treatment of this disease is not yet defined.

The main indications for both drugs have been mentioned. There are others which remain to be fully explored. These include among specific infections, whooping-cough and intestinal infections other than enteric fever, with particular reference to the possibility of abolishing the carrier state as well as alleviating the acute stage. Among less well-defined conditions are septicæmia, meningitis, pulmonary suppuration and urinary tract infections in which Gram-negative organisms are concerned. Here the problem is to assess the relative merits of the two new drugs and of streptomycin.

In any such studies we have a duty to remember that whereas streptomycin and chloromycetin are both manufactured in this country, aureomycin has all to be paid for in dollars. Hence a particular interest we have is to determine how far one of the other drugs can be made to serve in its place.

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Dr. John Crofton, *Postgraduate Medical School of London.*

The emergence of streptomycin-resistant tubercle bacilli is the outstanding disadvantage of this drug in tuberculosis.

It is now usually accepted that a minute proportion of resistant bacteria is present in cultures obtained from a patient before treatment. It seems likely that these resistant forms arise from the streptomycin-sensitive bacteria by a genetic change which can be regarded as a mutation. There are two main reasons for suggesting this. Firstly. the resistant bacteria breed true; reversion to sensitivity is very unusual if it occurs at all. Secondly, there is no increase of resistant bacteria in the presence of streptomycin unless the bacteria are in a medium which enables them to multiply. During treatment of a case of pulmonary tuberculosis with streptomycin the proportion of resistant tubercle bacilli increases. When the proportion of resistant to sensitive bacilli is roughly 1/50 to 1/2500 the culture shows as resistant in the ordinary routine tests when read at ten days (Mitchison, 1950*a*). Eventually the whole population of tubercle bacilli in the patient may become streptomycin resistant (Pyle, 1947; Mitchison, 1950*b*). In Gram-negative bacteria the mutation rate of sensitive to resistant forms is said to vary from species to species and there is said to be an inverse relationship between this rate and susceptibility to streptomycin *in vitro* and *in vivo* (Alexander *et al.*, 1949). Whether the mutation rate varies from strain to strain of tubercle bacilli is uncertain though there is a little evidence to suggest that the rate may differ in strains derived from different patients, and that this may be related to the ultimate emergence of resistant tubercle bacilli as measured in the routine tests for streptomycin sensitivity. But bacteria which have become streptomycin resistant may become so in varying degrees and the proportions of bacilli in pre-treatment cultures with different levels of streptomycin resistance would obviously be of great interest. The evidence on the point is tenuous (Yegian and Vanderlinde, 1948; Meads and Haslam, 1949), but such as it is it suggests that slightly resistant forms are more frequent than moderately or highly resistant, but that moderately and highly resistant forms are about equal in frequency.

The genetic basis of mutation to various degrees of streptomycin resistance is uncertain, but there is enough evidence to make some suggestions. It is worth recalling

Demerec's theory (Demerec, 1948) of the genetic basis of acquired penicillin resistance (Fig. 1). If sensitive bacteria are cultured into a series of tubes containing ascending concentrations of penicillin they can only be rendered highly resistant by a series of subcultures, subculturing on each occasion from the highest tube in which there is growth. By this means the bacteria become slightly more penicillin resistant at each subculture and eventually reach a high grade of resistance. Demerec suggests that there are a series of genes of roughly equal potency, a mutation in any one of which is capable of giving rise to a slight increase in penicillin resistance. The chances are that mutations in significant numbers will occur in only one gene at each subculture, so that at each successive culture organisms emerge with slightly increased resistance. If the subculture is made from the tube with the highest concentration of penicillin, then the initial population of bacteria will have one mutated gene so that in the next subculture there is a good chance of a second gene mutating, giving a further rise in resistance. And so on. If this experiment is repeated with streptomycin the results may be very different (Fig. 2). In any subculture there may be sudden leaps of resistance

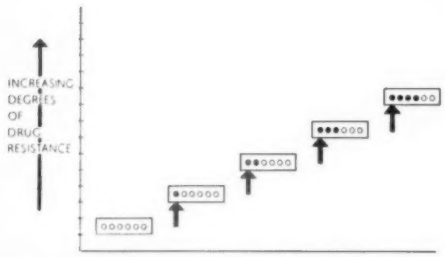


FIG. 1.—Suggested mechanism by which bacteria become penicillin-resistant. The rectangles symbolize bacteria; the white circles indicate equipotent genes which are shown as black after mutation.

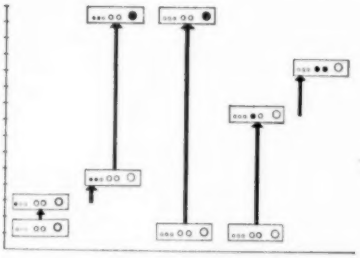


FIG. 2.—Suggested mechanism by which bacteria become streptomycin-resistant. The circles representing the genes are of different sizes, the smaller circles indicating genes of low potency the larger genes of higher potency.

to high levels. It is suggested that the facts are consistent with resistance being due to a number of genes of different degrees of potency. A mutation in some genes will produce bacteria of low resistance, a mutation in others of moderate, and yet in others of very high degrees of resistance. The low-potency genes are probably more numerous, and therefore more likely to mutate and produce bacteria with low degrees of streptomycin resistance, but every now and then a mutation will occur in a high-potency gene, with the consequent emergence of highly resistant bacteria.

Such a mechanism would account for the suggested distribution of bacteria with different degrees of resistance in pre-treatment cultures. It would also imply that the larger the bacterial population and the more rapidly it is multiplying the more likely are the rare mutations to highly resistant forms to occur. It is theoretically possible that exposure to streptomycin might increase the general mutation rate in a non-specific manner, just as unfavourable conditions increase the mutation rate in plants.

In both the series of cases of pulmonary tuberculosis treated with streptomycin with which I have been associated there has been a clear relation between the time at which streptomycin-resistant tubercle bacilli were first isolated and the degree of streptomycin resistance which was eventually attained (Crofton and Mitchison, 1948; Bignall *et al.*, 1950). The earlier that resistant tubercle bacilli were isolated after starting treatment the more highly resistant these bacilli eventually became. This was not because they had longer to become highly resistant, for the organisms attained

their final level of resistance relatively rapidly. This finding again is consistent with the conception that the more rapid the multiplication of the bacilli and the larger the bacterial population the more likely are mutations to occur in highly potent genes. In consequence the more likely are highly resistant forms to emerge, and the more likely are they to emerge early.

Evidence is accumulating that clinical factors may be correlated with emergence of streptomycin-resistant strains of tubercle bacilli. In cases in which the radiograph shows cavitation, there is a much greater likelihood of streptomycin-resistant tubercle bacilli emerging than when no cavity is demonstrable. Fig. 3 is derived from several American series (Mitchell, 1949; Howard *et al.*, 1949; Howlett *et al.*, 1949) and speaks for itself. In a recent series (Bignall *et al.*, 1950) we have found a correlation between the degree of confluence of shadows in the radiograph and the time of emergence of streptomycin-resistant organisms. The more confluent the shadows the earlier resistant forms emerge. It is worth stopping a moment to consider whether the actual physical condition in the lung, as instanced by cavitation and confluence, may directly influence the emergence of tubercle bacilli (Fig. 4). If streptomycin penetrates

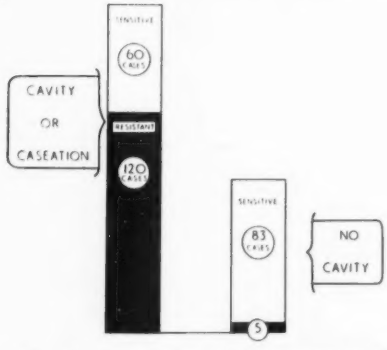


FIG. 3.—Comparison of the proportion of cases from which streptomycin-resistant tubercle bacilli were isolated in those with and without cavitation or caseation on the radiograph. The figures are derived from three different series (Mitchell, 1949; Howard *et al.*, 1949; and Howlett *et al.*, 1949), in which the criteria were slightly different.

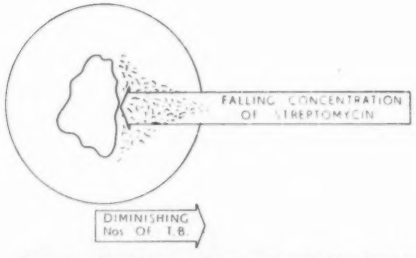


FIG. 4.—Possible mechanism by which physical conditions in the lung might affect the emergence of streptomycin-resistant tubercle bacilli. The large circle represents an area into which streptomycin penetrates poorly.

poorly into certain areas of the lung it may be that in the centre of these areas there is a rapid multiplication of tubercle bacilli with a consequent production by mutation of streptomycin-resistant forms. As forms of higher and higher degrees of streptomycin resistance emerge they will become capable of growing out along the gradient of increasing streptomycin concentration until eventually they may become capable of growing in contact with full concentrations of streptomycin.

We have found an indefinite but slightly suggestive correlation between the general clinical severity of the case and the emergence of resistant organisms (Bignall *et al.*, 1950). There are many exceptions to this trend but often very ill patients do produce tubercle bacilli with high degrees of streptomycin resistance and patients who are initially relatively well are a little less likely to do so. It seems possible that both these factors and the physical condition in the lung may be related to the emergence of streptomycin-resistant bacteria only in so far as they reflect the size of the bacterial population and the rate at which it is multiplying.

We have found that if routine examinations of the sputum are made in a patient with pulmonary tuberculosis under treatment with streptomycin there is usually an initial drop in positivity followed by a later rise (Crofton and Mitchison, 1948; Bignall *et al.*, 1950). If this drop does not occur it is nearly always an indication that highly streptomycin-resistant tubercle bacilli will emerge. But the converse is not true, as resistant organisms may emerge even though there is a significant drop in positivity. After the drop in positivity, unless the patient becomes permanently sputum negative, there is usually a later rise. When this has occurred it is found that streptomycin-resistant forms have emerged. It is interesting that this later rise will occur even when the tubercle bacilli have shown only a very slight increase in streptomycin resistance. This suggests that even low degrees of resistance may be of some clinical importance. But they are probably of less clinical importance than high degrees of resistance, because we have found that eventual sputum conversion is much commoner in those patients from whom only tubercle bacilli of low degrees of streptomycin resistance have been isolated.

Two main methods have been employed in an attempt to prevent the emergence of streptomycin-resistant tubercle bacilli. The first method is to give streptomycin intermittently. We have tried giving it in alternate weeks or alternate months with no success. It seems possible that giving 1 gramme every third day may delay the emergence of streptomycin resistance in a proportion of cases (Tucker, 1949) but further work needs to be done on this. The second method is by combining other drugs with streptomycin. So far the only drug which appears to be of indubitable value in this respect is para-aminosalicylic acid (Medical Research Council, 1949).

Many of the ideas and much of the work on which this paper is based are derived from other members of the group with which I have been associated. In particular I would like to thank Dr. P. D'Arcy Hart, Dr. Marc Daniels and Dr. J. R. Bignall of the Tuberculosis Research Unit of the Medical Research Council, Dr. J. W. Clegg of the Brompton Hospital, Dr. B. J. Douglas Smith and Dr. H. D. Holt of Colindale Hospital, and Dr. D. A. Mitchison of the Post-graduate Medical School of London.

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Professor Clifford Wilson, *London Hospital.*

Therapeutic trials of streptomycin in non-tuberculous infections have been carried out during the past three years under the auspices of the Medical Research Council. A preliminary report has been published (Wilson, C., 1948, *Brit. med. J.* (ii), 552) and subsequent work has confirmed and extended these results. With the introduction of aureomycin and chloromycetin the indications for streptomycin in

non-tuberculous infections have become more restricted, but at the present time there is insufficient information to assess the relative merits of the three antibiotics. The disadvantages of streptomycin compared with the new drugs are the necessity for treatment by injection, its toxic effects and the development of resistance to streptomycin by many bacteria. Streptomycin finds its chief use in infections due to Gram-negative bacilli and penicillin-resistant cocci. It is still probably the drug of choice in *H. influenzæ* meningitis in combination with sulphadiazine. It gives favourable results in other forms of penicillin-resistant pyogenic meningitis, particularly those cases developing after brain operations. In penicillin-resistant bacterial endocarditis streptomycin is ineffective alone and should probably be used in combination with other antibiotics. In septicæmia without endocarditis, especially due to *B. coli* or *Ps. pyocyanea* it is usually effective. In the large field of urinary tract infections it is likely that the newer antibiotics will supersede streptomycin owing to the frequent development of resistance to the latter. Streptomycin may still be the treatment of choice, however, in proteus and pyocyaneus infections. Results of streptomycin therapy are disappointing in respiratory tract infections although in *Friedländer* or *H. influenzæ* infections it is still probably the most potent antibiotic. Aureomycin should always be employed in penicillin-resistant staphylococcal infections. In view of its toxicity, streptomycin should never be used without expert bacteriological control and the closest co-operation between clinician and bacteriologist is essential before and after instituting treatment with the drug.

Section of Surgery

President—DIGBY CHAMBERLAIN, Ch.M., F.R.C.S.

[*March* 1, 1950]

DISCUSSION ON CONSERVATIVE RESECTION IN CARCINOMA OF THE RECTUM

Professor F. d'Allaines (Paris): It is now almost twenty years since I first undertook conservative surgery for cancer of the rectum.

The idea of sphincter preservation is certainly not new. Lisfranc had the idea of it in 1829, and the names of Kraske, Hochenegg, and recently Goetze, Finsterer and Mandl are well known.

In the light of recent anatomico-pathological studies we now know that there is very little danger of local recurrence in the region of the sphincter provided that the resection has been sufficiently high. The operation of conservative resection of the rectum may be entirely compatible with the complete preservation of the sphincter.

It is because of these studies of glandular invasion that we have again started conservative operations.

It is important to distinguish between two varieties of tumours in the rectum:

(A) *The high intraperitoneal tumours* situated at least 10 cm. from the anus. The lymphatic invasion occurs upwards through the upper hæmorrhoidal pedicle. In fact the anatomical work of Poirier and Cunéo, of Villemin, Huard and Montagne, and of Mondor has shown that the lymphatic propagation develops along this upper pedicle from the base upwards towards the gland placed within the fork formed by the superior hæmorrhoidal artery.

A study of the parts at operation confirms this important fact. Out of 210 invaded glands, Westhues finds 209 of them above the tumour, and one only on a level with the lower edge of the latter. Gabriel, Dukes and Bussey, in 1935, studied one hundred post-operative specimens and examined 2,000 glands. Dukes in 1940 analysed one thousand cases of cancer of the rectum. As a result cancer of the rectum has been classified into three varieties, A, B, C, and our previous ideas of the wholly ascending flow of lymphatic invasion have been confirmed.

The exceptions to this rule are very rare and due to the massive blockage of highly placed glands by the metastases in very advanced growths. Wood and Wilkie have noted cases of this kind. Glover and Waugh point out that even in these advanced cases retrograde extension only occurs in 1%.

Therefore it is agreed generally that the direction of the lymphatic flow is upwards towards the upper hæmorrhoidal pedicle. It is the same with the venous flow where the rarer metastatic thromboses occur upwards, as Dukes has found in 18% of the examined specimens. Since venous propagation might be responsible for double cancers of the rectum, it is necessary to resect widely the upper parts of the intestine (about 15 cm. above the tumour). The submucous lymphatic extension also occurs in the same direction and lower metastases are unknown at some distance from the tumour. Therefore, I think that in highly placed tumours of the rectum, the intestinal and glandular resection must be extended upwards for a sufficient distance to be certain of ablating these proximal extensions of the growth. On the other hand one may, without any danger, be conservative downwards.

(B) *Tumours below the peritoneal reflexion* lend themselves much less to conservative surgery, the proximity of the sphincter making conservation of the latter more dangerous; and the presence of the middle hæmorrhoidal vessels indicates the possibility of lymphatic metastases towards the pelvic wall in the lateral direction.

Indeed we know that the middle vascular stream is accessory and that its invasion is probably a later phenomenon, secondary to that of the upper lymphatic vessels. It remains true, however, that except for very early forms (Class A) conservative surgery seems illogical and dangerous for the subperitoneal tumours of the middle rectum.

To conclude, I think that the extirpation of a cancer of the rectum must fulfil the following conditions: in its upper part, the intestine must be resected widely. I have fixed the figure at 15 cm. above the upper edge of the tumour; the glands must be removed beyond the bifurcation of the superior hæmorrhoidal artery, and obviously still higher if an adenopathy is perceptible on the pedicle of the lower mesenteric artery. On the sides one must remove all the cellular tissue possible to achieve a real clearance of the pelvic cavity. However, in the lower part I think it necessary, but perfectly sufficient, to resect the intestine down to 5 cm. below the lower edge of the tumour.

Experience has proved me right. In the early days I observed three recurrences of cancer in the intestine which had not been resected; they were cases in which I had excised only 2 to 3 cm. from the tumour. Since I have insisted upon the rule of 5 cm. below the lower edge I have not observed any recurrence of cancer on the intestine except in 2 other cases in young subjects (29 and 32 years old).

Indeed in young patients the dissemination of the neoplastic cells is such that one must be very cautious in advising conservative surgery.

Indications for the Conservative Operation

To my mind every tumour of the rectum situated at 10 cm. or more above the anal orifice justifies sphincter conservation.

The section is thus made at 5 cm. below the tumour, and the anal canal remaining at least 5 cm. long allows a correct operation to be performed. However, other surgeons place the limit of the section much nearer the tumour: this margin of safety of 5 cm. is narrowed by some English and American surgeons down to 2 cm. (Pannett), 3 cm. (Wangensteen), 3 cm. (Babcock and Bacon). As I have already said, experience has shown us that it is prudent to resect more below the tumour.

Conservative resection of the rectum makes it necessary to have a rather long colon; this is easy in the case in which the normal sigmoid colon can be prolapsed, but if the colon is short it is necessary to mobilize the splenic angle of the left colon. This manœuvre always renders possible the placing of the colon down to the perineum.

I do not think that either the general condition or the age of the patient or the extension of the tumour contra-indicates conservative resection. When the radical operation is possible conservation of the sphincter depends on the site of the tumour.

Of course, at the beginning I was cautious, reserving this operation for the best cases, but now the ages of my operated patients range from 26 to 82 years and I have extended the operation even to cancers which have spread beyond the limits of the rectum (small intestine, prostate, bladder, vagina, ureter, solitary hepatic metastasis, and so on).

Thus there has been an increased proportion of operable cases among the patients examined since the beginning of my practice. At the beginning, only 60% of those examined underwent a radical operation. But, during the last two years, out of 131 examined cancers of the rectum, 117, that is to say 89·3%, have undergone a radical operation.

That applies to all radical operations, but among those 117 operations, 78 (66·6%) have benefited by the resection with sphincter preservation, and 39 (33·3%) have undergone a mutilating amputation.

Thus two-thirds (66·6%) of the operations were conservative, a figure which corresponds closely to the situation of the neoplasm. In two-thirds of the total cases the growth was situated at 9 cm. from the anus or higher. In only one-third of the cases was it below that limit.

Principle of the Conservative Operation

The essential principle of the operation is to preserve intact the function of sphincter control.

To obtain the best results it is necessary to preserve the sphincter, with, on each side, the levator muscles of the anus, the mucous tissue of the anal canal which is the origin of the reflexes of automatic control, and the vessels and nerves on each side.

I have used Kraske's method in 202 cases, i.e. the sacro-abdominal approach. By that method with the lower perineal phase, the operation is above the level of the levatores ani, and the whole sphincter region with the vessels and nerves is consequently preserved, all the operative manœuvres taking place above them. The suture is made between the left colon and the upper part of the anal canal; all the anosphincteric region is thus automatically preserved.

More exceptionally (40 cases) I have used Babcock's technique; the latter, derived from Hochenegg's, consists, after detachment of the mucous tissue of the anal canal, in invaginating the left colon within the anal sphincter. This method has seemed to me, as to many other surgeons, to offer a much less satisfactory control and I have used it very seldom.

I have never tried the conservative resection of cancer of the rectum purely by way of the abdomen (Wangensteen); I keep this operation for the treatment of cancer of the pelvic colon, in which, after resection, both intestinal ends are still covered with the peritoneal serous membrane. In cancer of the rectum in which the dissection inevitably leads into the subperitoneal space, on an intestine devoid of serous membrane, I think that one must use the double way with an abdominal phase and lower subperitoneal phase.

Sacro-abdominal Operation

I have resected 202 rectal cancers by the sacro-abdominal method.

In the early cases my technique varied, but now it constantly presents the following pattern

in two stages. The abdominal stage involves exploration of the lesions and of the whole abdominal cavity. Any tumour localized between the bottom of the pouch of Douglas and the promontory justifies conservative resection. The abdominal stage involves the liberation and the dissection of the tumour and the rectum above and below the growth. This liberation must be conducted up to the floor of the pelvic cavity with section of the vascular pedicle and lateral ligaments. However in difficult cases (big tumour, &c.), because of the large space afforded by the transsacral approach, one leaves all the subperitoneal operative manœuvres until the perineal stage.

The liberation of the colon must be conducted very widely to allow the latter to go down to the anus. About once in twelve times it is necessary to mobilize the splenic angle of the colon. Finally one marks out the point of division of the colon at a point at least 15 cm. from the upper edge of the tumour, and on that level the ligatures are applied for hæmostasis and prolapse.

I always peritonealize the pelvic cavity very carefully about the freed colon which is passed down into the bottom of the pelvis. In some cases in which the volume of that intestine hinders the peritonealization, this process necessitates a third stage after the perineal phase.

Finally, the abdominal stage ends with the placing of a temporary immediate artificial anus, intended to protect the sutures from the passage of the fæces. This artificial anus must stay between three and five weeks; it is very likely that it often proves useless but, however, I think it safer to make one in every case.

The second or lower stage implies a posterior incision which begins from 2 to 4 cm. behind the anus and extends more or less according to the difficulty. In the best cases, that is to say when I have been able to liberate the rectum down to the levator muscles, a 5 to 8 cm. incision is sufficient, with resection of the coccyx, but in difficult cases I resect the lower part of the sacrum up to the third sacral foramen. By this incision I exteriorize the colon and the tumour and I complete the liberation of the rectum.

These operative steps are all above the levatores ani which are not even seen.

For the colo-anal or colo-rectal suture, according to the height of the preserved rectum, I have used various methods. The one I have found the most satisfactory has been described by me in various articles.[1]

After anal dilatation, the preserved ano-rectal canal is exteriorized by prolapsing it through the anus and the colon is brought down into it. Both intestinal cylinders are thus brought down, one into the other, out of the anus, and united by a circular suture with interrupted stitches. As we have already mentioned a temporary colostomy avoids the parting of the suture, the perineal wound being completely closed round a pelvic drainage tube.

Babcock's Operation

I have followed almost exactly the well-known technique described by Babcock and Bacon. However, I add to it a pelvic peritonealization. I avoid the section of the anal sphincter in the posterior median line, except in the particularly difficult cases (volume of the tumour, fixity, &c.).

Post-operative Treatment

Of course, those operations are conducted after a careful preparation of the intestine for a week, with regular laxatives, non-residue diet and local disinfection by sulphonamides.

I attach special importance to the general biological study of the patient, particularly to the preparation against the deficiency of the blood proteins which play an important part in the healing of wounds. All our patients are submitted to a general anti-infective and vitamin treatment in all cases of ulcerated tumours.

The anæsthetic, administered under the direction of Dr. du Bouchet, is most often by Pantocain caudal block anæsthesia. However, we use general anæsthesia for elderly patients with a weak heart: ether, oxygen, curare, with intubation.

Results

As we shall see, the results are better after the sacro-abdominal operation than after Babcock's, but in defence of that operation I must confess that having known it only since 1944, the number of cases is more limited, and I tend to reserve it for the worst cases.

(A) *Operative mortality.*—202 *sacro-abdominal operations have given me an immediate post-operative mortality, within a fortnight, of 14 cases, that is to say 6·9%.*

The deaths were due to: cardiac failure (4), pulmonary complications (2), pulmonary embolism (1), profuse secondary hæmorrhage (1), urinary complications (1), septicæmia (2), post-operative shock (3).

[1] d'Allaines, F., Le Traitement Chirurgical du Cancer du Rectum. Paris, 1946.

The last three deaths occurred before the use of antibiotic drugs and modern treatment for shock.

Late post-operative mortality between three weeks and four months was 10 *cases, that is to say* 5%—rapid pulmonary metastasis (1), cachexia and general bodily decline with progress of the disease (4), various causes (5).

For comparison, here are the mortality figures after non-conservative amputation of the rectum:

101 *cases*: immediate mortality 17%, late mortality after three weeks 6%.

42 *Babcock operations* performed in four years, have given an *immediate mortality within two weeks of* 4 *cases, that is to say* 9·5%, *and a late mortality of one case, that is to say* 2·3%.

On the whole, those figures are comparable with the previous ones; the deaths after Babcock's operation have been due to: post-operative shock (1), severe pelvic hæmorrhage (2), gangrene of the prolapsed colon with pelvic infection (1).

(B) *Late survival.*—These results are almost identical after the sacro-abdominal or the Babcock operation, as is only to be expected, as the resection is about the same extent in both operations.

These are the figures after deduction of post-operative deaths:

Sacro-abdominal operation

After one year:	178	operated patients:	152	recoveries:	85%
„ three years:	132	„ „	73	„	55%
„ five years:	64	„ „	32	„	50%

Babcock operation

After one year:	37	operated patients:	25	recoveries:	67·5%
„ two years:	32	„ „	18	„	56%
„ three years:	22	„ „	12	„	54%

For comparison, after the classical abdomino-perineal operation with removal of the sphincter, the figures of survival are: After one year: 60%
„ three years: 50%
„ five years: 35%

Those figures are definitely less favourable, but I think they are due, not to the technique but to the fact that I have practised amputations for low tumours which are indisputably more serious, more liable to recur, and more metastatic than the high located tumours.

In fact the percentage of recovery, after sacro-abdominal operations, would appear to be more favourable, but my experience of the Babcock operation is too recent to allow me to reckon the successes after five years, and again I reserve the Babcock operation for the worst cases.

(C) *Functional results*: *Sphincter control.*—I have classified the results into three sections.

(*a*) *Excellent results*: Those are the patients who have retained perfect natural control for gas and fæces without artificial aids of any kind.

I should point out, however, that some of these patients show a frequency of stool during the first year, up to six a day. This decreases after a while and does not worry them much as there is no incontinence.

(*b*) *Fair results*: Control is good for solid matter, moderate for fluids. The patient wears an apparatus and sometimes uses washouts.

In general, however, he declares himself satisfied and prefers his slight infirmity to the establishment of an artificial anus.

(*c*) *Bad results*: There is complete incontinence. Some people bear it patiently, others ask for an abdominal artificial anus.

Sacro-abdominal operation

After the sacro-abdominal operation, the sphincter control is generally quite satisfactory.

Of 178 observed cases (that is to say: 202 – 24 early or later deaths):

Excellent results:	138	(77·7%)
Fair results:	34	(19·0%)
Bad results:	6	(3·3%)

Babcock operation

Comprising 42 cases minus 5 deaths:

Excellent results:	4 cases	(10·8%)
Fair results:	22 „	(59·5%)
Bad results:	11 „	(29·7%)

Amongst the 11 bad results, we include 4 cases of gangrene of the prolapsed colon which caused multiple fistulæ and required three permanent colostomies and a temporary one.

As I have already mentioned, *my results as to sphincter control are not in favour of the Babcock operation.*

Artificial anus: Fistulæ.—The sacro-abdominal operation may bring two unhappy results: a temporary artificial anus and fistula of the anastomosis.

Temporary artificial anus.—It is very necessary to protect the sutures from the passage of the fæces and avoid the fistulation of the anastomosis.

I know that some surgeons do without a colostomy but for many remarkable successes thus achieved there are some painful failures. But I have changed my practice on that particular point. The artificial anus is no longer kept for three months. Often it is only partially opened. About the twelfth day, if all goes well, I let the colon get little by little into the left iliac fossa and all is reduced to a slight operation of closing a lateral colostomy by the fourth or fifth week.

Fistulæ of the anastomosis.—There are two kinds of post-operative fistulæ; some are due to the *partial bursting of the anastomosis, through infection or patchy gangrene.* With an improved technique (accurate, close stitching), with the use of general and local antibiotics, owing to the complete closing of the perineal wound and the suppression of dead space by the gentle lavage of the anastomosis, we have succeeded in considerably diminishing the frequency and the size of these fistulæ.

The slight fistulation of the anastomosis (through which some injected liquid escapes) still exists rather frequently (about one-tenth of the operated patients), but it closes within one to three weeks. There remain the fistulæ kept up by a stenosis or a stricture of the anastomosis.

With dilatation of this stricture, or by means of an indwelling tube or eventually a new operation, I have always had good results.

I must confess that these last two fistulæ necessitate prolonged treatment, and need all the patience of the surgeon and of the patient, but they always heal at last on condition that the artificial anus be maintained during all the time required.

Of all my operated patients re-examined, only 2 still have a fistula (a woman suffering from severe diabetes, who refused a further operation, preferring to keep her artificial anus, and a man of 82 who had developed gangrene of the colon, and in whom I thought it safer to keep the artificial anus).

The second variety of fistula is due to massive gangrene of the colon.

This complication is hard to foresee as it may occur with patients whose prolapsed colon was bleeding satisfactorily in the peritoneal phase. It brings a complete obliteration of the retracted colon, with a fistulous track leading down to it, and in most cases a permanent artificial anus must be maintained. I have seen 4 cases after the sacro-abdominal operation, 2 in patients with a liver metastasis at the time of the operation, and 2 in patients aged 72 and 78 years.

Massive fistulization is not peculiar to the sacro-abdominal operation, I have also seen it four times in Babcock operations, compelling me immediately to establish a permanent artificial anus.

Conclusion

I consider that the conservative operation is of the greatest importance in the treatment of cancer of the rectum. Our primary object, when dealing with a malignant tumour, is to secure a lasting recovery, but it is none the less essential to avoid a painful disability for the patient whenever possible.

However, the conservative operation must not be performed in unsuitable cases (low tumours, young subjects, and so on). The possibility of avoiding the artificial anus in three-fourths of the cases in the treatment of cancer of the rectum should persuade patients as to the value of early operation. As long as operation is the most efficient treatment, it is the only course to follow.

Mr. C. Naunton Morgan, F.R.C.S. (London): In the treatment of cancer of the rectum with preservation of the sphincter mechanism, restorative methods are not new, indeed they antedated amputation of the rectum by half a century.

Professor d'Allaines has mentioned Lisfranc in 1826, and I would like to add the name of Reybard of Lyons who in 1833 did the first resection of the sigmoid colon with anastomosis. It is reported that this surgeon was severely criticized by the Paris Académie de Médecine, as, I fear, we may be in the Royal Society of Medicine nearly one hundred and twenty years later. Verneuil, another Frenchman, revived interest in rectal excision with preservation of the sphincters, in the last quarter of the nineteenth century.

Owing to the high mortality rate of any abdominal procedure at this time the first attempts at excision of the rectum, with or without restoration of continuity, were by a perineal or para-sacral approach.

In 1885, Kraske introduced a method in which, by excision of the coccyx and part of the

sacrum, a wide exposure of the perineal rectum was obtained and, in 1889, Hochenegg described the pull-through operation in order to obviate formation of a fæcal fistula.

These operations did not gain much popularity in this country, owing to sepsis, faulty union and fistula formation. Yet in 1888, William Allingham described a method in which the external sphincter was preserved, and, in 1904, at the Royal Medico-Chirurgical Society, Sir Frederick Wallis showed a case of carcinoma of the rectum treated by ano-coccygeal resection; a method he recommended for growths situated higher than 3 in. from the anus.

At the turn of the century, surgeons contemplated the combined abdominal and perineal approach and Quenu in 1898 described a two-stage abdomino-perineal operation. Kraske, too, had now become an advocate of an abdomino-sacral method.

A combined abdominal and anal operation was described in August 1892, in the *Lancet*, by Maunsell, late of New Zealand. This method was modified in 1901 by Weir of New York, and is similar to that used occasionally at St. Mark's Hospital to-day for certain cases to be mentioned by my colleague, Mr. O. V. Lloyd-Davies.

In 1903, Sir Charles Ball, in his last Erasmus Wilson lecture, advocated the abdominal approach and in the same year Dame Louisa Aldrich-Blake, a great surgeon, described an abdomino-perineal operation with preservation of the sphincters.

As a result of the important and brilliant work of Ernest Miles on the spread of carcinoma of the rectum in 1908, little interest in restorative procedures was shown either in this country or America, though the continental surgeons continued in their efforts to avoid a colostomy. Sporadic attempts (at restoration of continuity) were made in 1908 by Lockhart-Mummery and Hamilton Drummond who described the tube method of anastomosis and by Archibald of Montreal who confirmed the opinion of Kümmel of Hamburg (1892), Treves and De Quervain, that the blood supply of the proximal colon could be conserved, and, in fact, the transverse colon and splenic angle, if needs be, could be brought down to the anus. Archibald's experimental work on the blood supply of the left colon was of great importance. He gave up abdomino-anal excision, however, owing to the risks entailed, but speaking thirty years later, in 1938, he said he believed that if infection could be controlled, and shock with attendant low blood pressure be avoided, restorative methods would finally find their place in the treatment of cancer of the rectum.

Following Miles, both in this country and in the United States of America, we have come to think of only one method of extirpation of cancer of the rectum, though there have been the minority in Professor Grey Turner, Professor Pannett (1935) and Rayner (1936) in England and in the United States of America, Babcock (1932), Horsley, Dixon, Bacon and Wangensteen who have revived interest in restorative procedures, and believe that in certain cases of carcinoma of the rectum continuity could be restored and a permanent colostomy avoided.

I think that most of us would agree that suppose there were only one operation available for cancer of the rectum, then combined excision would be that operation.

We all know that patients will adapt themselves to an abdominal colostomy and live useful and unhandicapped lives, but unfortunately all our patients are not like one of Reverdin's who being satisfied with her colostomy said to him " Je ne comprends pas que le bon Dieu ne nous ait pas mis le derrière devant; c'est bien plus commode" (quoted by Archibald). However, there are patients and circumstances where if a colostomy could be safely avoided, much happiness would be the result. None of us can honestly say that life with a colostomy is desirable, unless it is an absolute necessity.

Because of increased and more accurate knowledge of the spread of cancer of the rectum, due largely to the work of Cuthbert Dukes, Gabriel, Bussey, David and Gilchrist and many others, to modern methods of pre- and post-operative treatment, to the advent of sulphonamides and antibiotic therapy in control of infection together with advances in surgical technique and anæsthesia, new interest has been aroused and the time has come for us to review the situation carefully.

Lymphatic Spread

We now know that apart from the constant upward lymphatic spread, extension along the lymphatics in other directions is unusual in growths that are not advanced or are not anaplastic.

Downward spread.—The degree of downward spread in the submucous layer of the bowel is very slight (a few mm.) and the occurrence of retrograde lymphatic involvement is uncommon. David and Gilchrist report lymphatic spread below the primary tumour as occurring in 4·3% of cases to distances of from 1 to 5 cm. and Glover and Waugh found that only in 1% of their series did this occur further than 2 cm. below the growth.

Our colleague, Dr. Cuthbert Dukes, has kindly carried out a preliminary analysis of 830 cases of carcinoma of the rectum operated upon by combined excision at St. Mark's Hospital between 1938–1943. This shows that downward spread either in lymphatics or veins occurs in approximately 4% of cases. Spread beyond 5 cm. below the lower margin of the growth

occurred only in 2% of cases. It is noteworthy that three-quarters of cases showing downward spread were found to be in tumours of high grade of malignancy. In the series of 110 restorative operations about to be reported, there were 5 with downward spread. Because of the possibility of downward spread, it has been our practice to divide the bowel and surrounding block of tissue 5 cm. below the lower margin of the growth as recommended by Professor d'Allaines.

Lateral spread.—It has not been fully appreciated that the pubococcygeal portions of the levator ani grasp the lower rectum and are applied intimately to its walls and do not lie as a diaphragm across the pelvic outlet. The pelvic fascia lying on the superior surface of these muscles also envelops this portion of the rectum. In this region, in addition to the constant upward lymphatic spread, there is a choice of spread laterally along the levators and pelvic fascia and the lymphatics accompanying the middle hæmorrhoidal vessels, and in growths in the lower third of the rectum, extension along the lymphatics accompanying the inferior hæmorrhoidal vessels.

From the data available in the literature, lateral spread is found to be more common in advanced cases where the upward lymphatics are blocked. However, there is evidence that this lateral spread will occur in less extensive growths situated low in the rectum.

The lower rectum lies more or less in a sealed compartment formed by the tough pelvic fascia and pubococcygei. In order to perform a restorative resection at this level, the compartment must be opened, with the risk of local recurrence (Fig. 1).

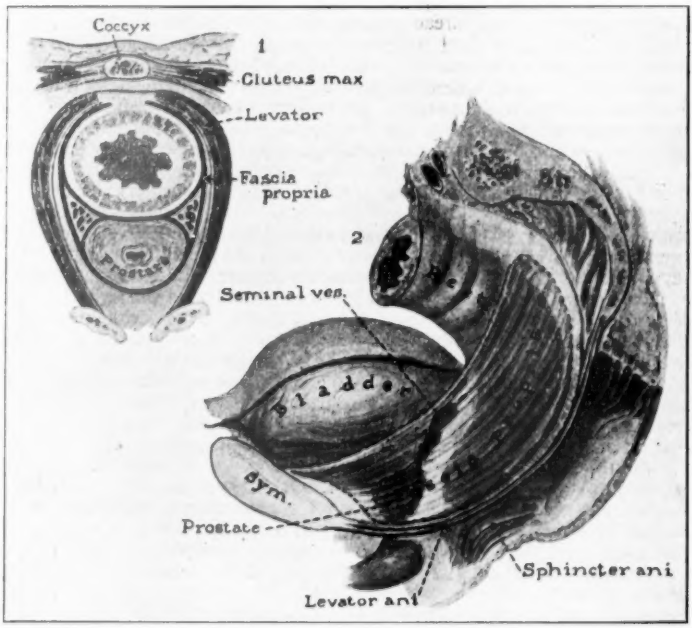


FIG. 1.—Relation of fascia propria to rectum and prostate. (1) Schematic cross-section showing continuation of fascia propria around the rectum and prostate. This fascia must be cut to allow separation of the rectum from the prostate. (2) Schematic lateral view of the bowel, showing the origin and extent of the fascia propria indicated by dotted line.

From Vernon C. David, in Dean Lewis's "Practice of Surgery", published by W. F. Prior Company Inc., Hagerstown, Maryland.

It is clear therefore that the only operation which will deal radically with growths in the lower two-thirds of the rectum must allow of wide excision of the levators and pelvic fascia. Since upward spread is a constant occurrence, a combined excision (or amputation) of the rectum is the only safe measure of dealing with such cases. No other operation will allow thorough removal of the pelvic floor musculature and fascia together with the upward field of lymphatic spread.

Upward lymphatic spread.—The importance of thorough removal of the upward zone

of lymphatic spread in all cases of carcinoma of the rectum, whatever the position of the tumour, is established. It must be realized that it is not so much the length of the colon above the growth that is excised that matters, as the length of mesentery removed and the height of the ligature on the inferior mesenteric vessels. It has been our practice to ligature the inferior mesenteric pedicle as high as would be done if a permanent iliac colostomy were to be established when performing a combined excision. My colleague will tell you of the level of ligature in all our cases. Having ligatured the inferior mesenteric pedicle at the high level, if then by judicious preservation of the paracolic arterial anastomosis the blood supply to an adequate portion of the colon can be retained, a restorative operation can be performed if the case is otherwise suitable, for only a small portion of the mesentery adjacent to the sigmoid colon will be conserved.

We consider that it is the height of the ligature on the inferior mesenteric pedicle and the wide removal of the mesentery that is important and not the amount of proximal colon excised, because recurrence of a growth higher in the bowel, due to venous spread, is unlikely, except in advanced or highly malignant tumours which should be treated by combined excision.

Incidence of Local Recurrence

The frequency of local recurrence even following radical combined excision of the rectum, especially with growths in the lower two-thirds of the rectum, has not been fully realized. In the male, local recurrence is often hidden in the closed pelvis following combined excision.

The intimate relation of the infraperitoneal rectum to the adjacent organs, the prostate and vesicles or vagina and, as already mentioned, to the pubococcygei and pelvic fascia must increase the chances of local recurrence of rectal growths in this situation. In fact, it has been our practice to remove the posterior vaginal wall routinely when performing combined excision in all cases where the growth involves the anterior rectal wall below the level of the peritoneal reflection, owing to the frequency of local recurrence at this site.

Though the peritoneal cul-de-sac is variable in position (5–10 cm. from the anus according to Kirklin, Dockerty and Waugh), in the average case, the peritoneal reflection (pouch of Douglas or rectovesical pouch) is an important landmark to the surgeon when, in addition, the distance of the lower margin of the growth from the anal verge is also taken into consideration.

The incidence of local recurrence following radical combined excision for growths *below* the peritoneum is much greater than for those situated *above* the peritoneum.

David and Gilchrist found that for subperitoneal carcinomata with lymphatic metastases (C cases), local recurrence occurred in 23% as compared with 3·6% local recurrence in tumours (C cases) situated above the peritoneal reflection. The comparative survival rate of growths (C cases) above the peritoneal reflection was 51% in five years, as compared with 37% in five years for growths (C cases) lying below the peritoneal reflection.

From a preliminary survey of 830 cases of the 3,000 case records available at St. Mark's Hospital in which the size, position of the primary tumour and its local, venous and lymphatic spread are graphically recorded, Dukes reports that in cases with lymphatic metastases, the survival rate is twice as good for growths above the peritoneal reflection as for those below it in the lower two-thirds of the rectum.

When there is no lymphatic involvement, though the position of the primary growth in the rectum does not affect so materially the survival rate, the results of excision of growths low in the rectum are slightly poorer than for growths lying higher up. Thus we reach the paradoxical conclusion that the worst place to have a carcinoma of the rectum is in its distal portion which one would have imagined to be a site more amenable to early diagnosis and treatment.

Wangensteen's experience is similar in that he found that restorative resection for tumours at 6–8 cm. inclusive from the anus, local recurrence occurred in 25% of cases, whereas when the growths were situated from 9–13 cm. from the anus, the local recurrence was 6·3%.

Local recurrence may not be primarily at the site of anastomosis, but first in the perirectal tissues, but we feel that at operation transplantation of malignant cells to the suture line from within the lumen of the bowel is a possibility. My colleague will tell you of our efforts to avoid this latter hazard.

We are thus in accordance with Professor d'Allaines' opinion that growths lying below the peritoneal reflection are unsuitable for restorative resection, for even in comparatively early growths there may be lateral spread. We also would agree that the local extent of the primary growth should be no bar to its extirpation as our operability rate (resectability) of 93% shows. In fact in the last 100 cases of carcinoma of the rectum, the operability rate has been 98%.

Because of these facts, those of our colleagues at St. Mark's Hospital, who have been prepared to consider procedures other than excision (amputation) for carcinoma of the

rectum have selected cases with special caution and each case has been considered individually before a restorative operation has been carried out.

To emphasize this selection, during the past few years we have been employing restorative methods, both radical and palliative in only 1 in 5 of all cases of carcinoma of the rectum.

Criteria for Radical Restorative Resection

(1) *Site of growth.*—The lower margin of the neoplasm must not be lower than 10 cm. (which is an arbitrary distance) from the anus and be above the peritoneal reflection. The height of a neoplasm as estimated on sigmoidoscopy, is often less than it appears owing to the rectal curves. It is noteworthy that the promontory of the sacrum in a male 5 ft. 10 in. tall, is about 17 cm. from the anus as measured with a sigmoidoscope. From an examination of 242 specimens fixed and pinned out, i.e. straightened specimens of bowel following combined excision, Bussey at St. Mark's reports that 127 have their lower edge less than 10 cm. from the anus, i.e. 52%. Thus about one-half of all cancers are unsuitable by reason of their position alone.

(2) *Size.*—If a growth is bulky or there is evidence of marked extrarectal spread, a combined excision is advised. The reason for this is the fact that there is an increased risk of local recurrence which might involve the anastomosis or retained bowel.

(3) *Histology.*—If there is either clinical or histological evidence that the growth is of the anaplastic simplex type, then it would be better in most cases to do a combined excision.

(4) *Build of the patient.*—In a short fat subject with a small pelvis and fat-laden mesentery the operation may be unwise.

(5) *The anatomy of the colon and its vascular arrangement.*—As a rule it is the length of the sigmoid mesentery and its vascular arrangement that will help to decide the advisability of attempting restoration of continuity. Shortening of the colon mesentery due to fat or diverticulitis or adhesions of the colon to the rectal growth may be a deciding factor, unless the transverse colon can be utilized.

Certain objections to restorative operations have been raised. Amongst them are the following: (*a*) Retention of a portion of colon or rectum which is a common site for the development of a second primary tumour.

This is a possibility in 4% of cases and it is admitted that unless the bowel is carefully palpated at operation a second primary growth or a polyp may be overlooked.

All cases of carcinoma of the colon should be carefully and regularly followed up, both clinically and radiologically, and it is even more necessary to follow up meticulously all cases of carcinoma treated by restorative operations, which are on trial, not only to detect local recurrence but the possibility of another primary tumour.

(*b*) *The operation is not radical:* Time will give us the answer though Dixon who has been practising restorative resection for years reports a survival rate of 67·7% in five years, and we congratulate Professor d'Allaines on his results.

Some of those who condemn these operations as not being radical are yet prepared to do a wedge resection of the sigmoid mesocolon for carcinoma in this portion of the bowel.

(*c*) *Mortality:* Restorative operations are time consuming but we have found that patients stand a prolonged intra-abdominal operation remarkably well if there is no added perineal phase. The mortality compares favourably with that of combined excision.

(*d*) *Morbidity:* There is an increased morbidity, but now by limiting the operation to the transperitoneal approach, persistent fæcal fistula or stricture formation are rare.

(*e*) *Poor sphincter control:* The operations to be described by my friend and colleague, apart from the Bacon and Babcock procedure which we have discarded, retain a normally functioning anal canal and a portion of the rectum, and control is normal.

In conclusion, because of the yet uncertain results of restorative methods these operations are performed only after very careful selection. We feel that, even if operations which preserve the delicate and undoubtedly pleasant and satisfying mechanism of defæcation are once again to be relegated to the failures and relics of the past, it will be shown that, as a result of modern methods, all carcinomata of the rectosigmoid will not require a combined excision for their radical extirpation. Further, intraperitoneal restorative resection will have a place in the palliative treatment of carcinoma of the rectum, provided cases are selected where local recurrence is unlikely before distant metastases end the scene.

I have discussed the problem of restorative surgery on the basis of general principles, to which I would add gentleness, maintenance of blood volume and blood pressure, avoidance of major soiling, careful suturing without strangulation of tissue or eversion of mucosa, and no tension at the suture line.

Now my colleague will tell you of the methods and results of the practical application of these basic principles in the cases from St. Mark's Hospital.

(*For* REFERENCES, *see* pp. 709, 710)

Mr. O. V. Lloyd-Davies, M.S. (London): My colleague and I are presenting this evening the cases of restorative resections performed by us and our colleagues at St. Mark's Hospital.

The series is not a large one, due as you have heard to our rather cautious approach to the subject.

There are two groups.

First: Combined restorative operations 29 cases comprising

Abdomino-sacral excisions	7
Abdomino-anal excisions	19
Bacon-Babcock operations	3

Second: The intra-abdominal rectal resection with anastomosis 81 cases.

The first operations we attempted were abdomino-sacral operations and later on abdomino-anal operations. Two-thirds of them were performed before the days of bowel chemotherapy and were three-stage operations:

In *Stage i* a transverse colostomy is performed at the exploratory laparotomy.

Stage ii is the resection and anastomosis.

Stage iii, closure of the colostomy.

In the two-stage operations a transverse colostomy or cæcostomy is performed at the time of the resection and anastomosis.

TABLE I

7 cases of abdomino-sacral operations

1 died bronchopneumonia eighth day

3 local recurrences occurred between six months and four years later
2 B V cases; 1 C1 case.

3 survivors over thirteen years: A B C1.

Of the results of this group of 7 abdomino-sacral operations, one died of bronchopneumonia on the eighth post-operative day.

Of the six survivors 3 died of recurrence. 2 of these were local recurrences in the region of the anastomosis noted six months and four years after operation and one developed a recurrence in the ovary and had general peritoneal deposits six months after operation.

The remaining 3 cases are alive and well to-day; over thirteen years later. One A case, one B case with slight extrarectal spread and one C1 case with extensive extrarectal spread.

We gave up these abdomino-sacral operations because of local sepsis and fistula formation between the anastomosis and the sacral wound.

It is likely that nowadays with modern antibiotics there would be fewer troubles but at that time our dissatisfaction led us to try another method: the abdomino-anal operation. This is an operation which we still perform but latterly have only used it as a palliative operation for cases with liver secondaries in which the tumour was too low to perform an intra-abdominal anastomosis.

In the abdomino-anal operation there is no perineal wound and an external fistula is avoided. The presacral space has, in most of the cases, been drained through the posterior part of the anastomosis but in the last 5 cases this space has been drained from above through the abdomen; we are not yet certain whether this is the better method.

The objections which we have to this operation are these:

First: The length of viable colon required is much longer than that required for an intra-abdominal rectal resection with anastomosis and in our small experience we have found difficulties in obtaining sufficient length of bowel in many cases. Admittedly this operation requires a slightly greater length of bowel than the abdomino-sacral method.

Second: The colon in either an abdomino-anal or abdomino-sacral operation frequently forms a bowstring between the pelvic brim and the anus and the resulting presacral space is accentuated; some very adequate method of draining it is necessary and septic complications tend to occur. There is also likely to be tension with possible thrombosis of the vessels due to pressure at the pelvic brim. When there is ample length of viable colon these troubles are much less since colon and peritoneal floor fall back into the presacral hollow and the space is rapidly obliterated by intra-abdominal pressure.

Because of these difficulties we tended to turn our attention in recent years to the possibilities of intra-abdominal restorative operations for rectal growths.

TABLE II.—ABDOMINO-ANAL CASES

Total 19. No deaths

3 palliative operations (liver secondaries)

16 radical operations

6 local recurrences

5 within four years — 1 A case; 1 B case; 3 C1 cases (A.P. excn. 1 case two years ago. A and W.)

1 six years later — A case along drain track

5 died

10 cases alive and well and over half of them have passed the five-year mark.

Reviewing the results of these 19 abdomino-anal cases: There were no operation deaths: 3 were palliative operations for patients with liver secondaries and of the 16 radical operations 6 developed local recurrences, 5 within four years and 1 six years later.

Of these 6 local recurrence cases, 5 are dead and in only 1 C1 case which recurred nearly four years after the resection was it possible to perform a combined excision operation. This was done two years ago and so far the patient is alive and well. I would, however, like to stress that the opportunity of giving a patient a reasonable second chance is in our present experience a very remote one. Of the remaining 10 cases all are alive and well: 2 over ten years; 4 over five years; 2 nearly four years. Recurrences occurred in 2 A cases; 1 B case; 3 C1 cases; and of this group the recurrences in the two A cases were a great disappointment to us.

We had felt that if only an A case could be diagnosed as such pre-operatively then surely some restorative operation was manifestly the operation of choice; in fact a local excision should be adequate. There was here no question of inadequate removal of the growth and its spread, but some other factor must have been at work.

There appear to be two possibilities.

First: the implantation of cancer cells extruded from the tumour and it is a fact that clumps of free cancer cells exist within the lumen of the bowel and it is common knowledge that transplanted cells can grow in the granulation tissue of a fistulous track.

Second: a traumatic factor caused by the suturing may result in stimulation of the rectal epithelium which in such cases has a predisposition to producing malignant change.

In addition to the abdomino-sacral and abdomino-anal operation there have been 3 Bacon-Babcock operations.

We have always felt on theoretical grounds that this operation would give unsatisfactory results regarding rectal continence and our aim has been to retain not only a normal anal canal musculature with its normal lining but also a small cuff of rectum. An independent investigation of bowel sensation and function carried out by our colleague John Goligher has confirmed the importance of doing this, and anorectal function has been perfect except in the 3 Bacon-Babcock cases, none of whom had rectal sensation or true control. One of these developed a local recurrence.

A review of the earlier cases was made by us at St. Mark's in recent years and a fresh and united attack made upon the problem. Account was taken of the impossibility of accurately determining the exact extent of spread of the growth and therefore the widest possible excision had to be performed.

Subperitoneal growths were excluded for the reasons already given by my colleague; but it was felt that a *well-conducted* restorative operation for growths situated above the peritoneum should give as good results as a combined excision provided that there was no increased morbidity.

Since November 1945 we have performed at St. Mark's a series of 81 intra-abdominal rectal resections with anastomosis for growths above the pouch of Douglas or rectovesical pouch; the average height of the lower edge of the growth by sigmoidoscopy has been 12·9 cm.

We decided (1) that a high ligation of the inferior mesenteric artery should be made at the site normally used in a combined excision leaving only the left colic or first sigmoid artery. In only 12 cases has the ligature been placed below this level and in half of these latter cases the operation was palliative.

(2) That a block removal of the bowel, its mesentery and surrounding tissues should be carried out in as wide a fashion as when performing a combined excision and the dissection continued downwards for 2 in. below the lower border of the primary growth: in order to be as certain as possible of being radical in all cases bearing in mind the 4% with downward spread.

(3) In an attempt to eliminate implantation of cancer cells we have carried out a careful toilet of the rectal stump after applying a clamp across the bowel 2 in. below the growth. The rectal stump has been irrigated with soda bicarbonate solution and 1:500 perchloride of mercury. This can be done quite easily with no disturbance to the operator provided the patient is in the lithotomy-Trendelenburg position.

The general plan of these intra-abdominal rectal resections with anastomoses has been as follows: All the cases are carefully prepared for at least five days before operation and the intestinal flora controlled with locally acting antibiotics.

It is always necessary to divide the congenital peritoneal folds on the outer side of the pelvic and iliac parts of the colon before a final decision is reached regarding the available length of pelvic mesocolon. In 2 cases the transverse colon has been anastomosed to the rectal stump.

When hepatic metastases are present some restorative operation is obviously very desirable and the criteria applicable to radical restoratives do not apply to the same extent. It must, however, be remembered that a local recurrence involving the anastomosis before liver metastases have produced the inevitable end may place the patient in a much worse position than he would have been in had a combined excision been performed. There have been 21 palliative operations in this series.

TABLE III.—INTRAPERITONEAL RECTAL RESECTIONS WITH ANASTOMOSIS

Total 81 cases

Average age 60 years	Range 34–80 years
60 radical operations	21 palliative operations
Dukes' classification	
A 14	Liver deposits 13
B 18	Peritoneal deposits 5
C1 22	Liver and peritoneal deposits 2
C2 6	Extensive malignant recto-vesical fistula 1
Growth in veins found in 6 cases	Growth in veins found in 8 cases

The next step is the division of the inferior mesenteric pedicle as for a combined excision with suitable ligatures proximal to the arcades.

Slides from our colleague John Goligher representing his findings on examining 75 post-mortem cases, &c., were then shown (1949).

The bowel is now mobilized as in the abdominal dissection of a combined excision to a level 2 in. (5 cm.) below the lower border of the primary tumour. When this is completed it is advisable to review the length of viable bowel and ascertain whether it is sufficient to reach the proposed site for division of the rectum and to perform an anastomosis without tension.

The mesentery of the rectum is now divided at the 2 in. (5 cm.) level and a right-angled clamp applied to the bowel.

Irrigation of the rectal stump now takes place, care being taken to see that all fluid is removed at the end of the process. Whilst this is going on the proximal colon is being divided at the selected site and its lumen carefully cleaned.

The rectal stump is then divided below the clamp and a wide end-to-end anastomosis made. It is important to make the division of the two opposing ends of bowel as oblique as possible and additional safety is obtained by rotating the colon so that peritonealized surfaces are applied to the non-peritonealized surfaces and the least vascular borders to the most vascular borders. In our experience it is wise to drain the site of the anastomosis transperitoneally in all cases.

A debatable point is the question of doing the operation in stages. In the early cases in he series caution led us to do many three-stage operations and in the first 20 cases there were 11 three-stage operations and 9 two-stage operations. In the last 30 cases there has been only 1 three-stage operation because of acute obstruction on admission: 6 two-stage operations and 23 one-stage operations. The change over has occurred as the result of increasing experience, improvement in technique and better bowel preparation.

The problem has, therefore, resolved itself into whether or not to do a proximal colostomy at the resection operation. When there has been any particular difficulty with the anastomosis, when diverticula are present in the proximal colon or when there has been poor bowel preparation it is wiser to do a proximal colostomy at the time. In fact if the surgeon is in any doubt a proximal transverse colostomy should be performed.

Although the total number of cases (81) is too small to give an accurate mortality rate the figures compare favourably with those for a combined excision series (Table IV).

TABLE IV.—INTRAPERITONEAL RECTAL RESECTION WITH ANASTOMOSIS

Total 81 cases

Including 21 palliative operations

Deaths 6 = 7·4%

	Cause
No. 1 age 70	Uncontrollable hæmorrhage, died six hours after operation.
,, 2 age 52	Perforated gastric ulcer. Died nineteenth day.
,, 3 age 80	Separation of anastomosis and pelvic abscess. Died twenty-fourth day.
,, 4 age 72	Pulmonary embolus. Died eighth day.
,, 5 age 47	Palliative case (liver and peritoneal deposits). Presacral hæmatoma. Separation of anastomosis. Retroperitoneal cellulitis and abscess formation. Died sixth week.
,, 6 age 70	Palliative case (liver deposits). Paralytic ileus. Coronary atheroma. Died tenth day.

In this group there were 6 deaths occurring within six weeks of operation (7·4%). In 2 of these death was definitely the result of this particular type of procedure.

The immediate operation complications were as follows (Table V). The incidence of sepsis in association with the anastomosis has been about 1:10.

TABLE V.—IMMEDIATE COMPLICATIONS IN 75 SURVIVORS

	Cases
(1) Temporary fæcal fistula along abdominal drainage tube (All closed spontaneously within ten days)	3
(2) Rectovaginal fistula (Closed spontaneously in one month)	1
(3) Pararectal abscess burst through suture line (No drainage used at operation)	1
(4) Posterior separation of suture line (Delayed healing)	1
(5) Stricture formation (None serious)	4
(6) Small intestinal obstruction adhesions to pelvic peritoneum (Relieved by operation on the thirteenth day)	1

Of the late complications there were 3 further cases of small intestinal obstruction occurring two to three months after leaving hospital. These were operated upon elsewhere and 2 of them died—one of these was a palliative case.

In a series of over 1,000 combined excision operations recently investigated the post-operative incidence of small gut obstruction occurring within five years of operation was about 4%.

Regarding the late results of the 55 radical cases surviving the operation for more than three months: 4 cases have developed recurrences—2 of them have been local pelvic recurrences and 2 have had distant recurrences.

These figures are too small and the time period since operation too short to give a really accurate picture of the local recurrence rate but in a few more years the situation will be clarified.

It may be remembered that in a preliminary survey two years ago I recorded (Lloyd-Davies, 1948) that we at St. Mark's Hospital had become aware of the dangers of restorative procedures particularly the high local recurrence rate in our early series.

Since 1945 we have been choosing our cases with greater care and are very mindful of the risks of transplantation.

We think to-day that we are justified in regarding a certain proportion of rectal growths situated above the peritoneal floor as suitable for radical restorative surgery, provided that the criteria already mentioned are carefully followed and over-enthusiasm does not distort the judgment of the surgeon.

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Section of Odontology

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Surgery and Prostheses

By Rainsford Mcwlem, F.R.C.S.

The correction of defects of contour or of support by prosthetic materials may be carried out in two ways. They may be implanted in the tissues or they may be fashioned into removable appliances. The former method has enjoyed a recent increase in popularity but it appears to me to be based upon principles which have no biological basis and to be not altogether devoid of unnecessary risk. No such use of prosthetics will be considered in this paper.

When removable appliances are considered, there are three ways in which they are most commonly used: (i) as an alternative to surgery; (ii) as a temporary measure until surgical restoration is possible; (iii) as an adjuvant to surgery.

In the first group the most obvious use of an appliance is in those instances in which the possibility of reconstruction is at present beyond the scope of surgical technique. The commonest example is loss of an eye. In many cases its replacement by a prosthesis will result in an almost normal appearance, but there are exceptions. When the lids have been so damaged as to reduce their mobility the effect of wearing an artificial eye is rather to attract attention to the condition than to disguise its presence. The patient, however, is not aware of this state for he sees himself only when his sound eye is open—he is unconscious of the fact that he does not blink or close the affected lids—and he can be made to realize the true state of affairs only by seeing a film of himself. It may sometimes be preferable to obliterate the eye socket completely rather than to attempt an ingenious prosthetic reconstruction.

Complete loss of the ear is another condition in which surgery does not as yet offer perfection of repair, although the results are steadily improving. An artificial ear may well have an excellent shape and appearance, but this advantage must be offset against the fact that it is a prosthesis, that it requires constant attention and that fixation is sometimes awkward. The latter difficulty may be overcome by the surgical provision of retention points—but even then the patient may well still suffer from a feeling of insecurity.

The choice between surgical and prosthetic restoration must always be made only after consideration of the individual factors present in every case.

A more functional use of an appliance occurs in cases of recent VII nerve paralysis. An immediate assessment of the probability of recovery cannot be made but if nerve regeneration occurs in the presence of overstretched muscles there will be loss of some degree of function. Early and effective support to those muscles which have been deprived of their innervation is essential. This can be done by surgery but it can also be done by an intrabuccal prosthesis. This is built up into the sulcus on the affected side and supports the angle of the mouth and also, to some extent, the lower lid. It does not correct the stretching of the affected half of the orbicularis but this is not always a marked condition and there are many cases in which such a simple procedure offers an efficient alternative to operation.

The second group comprises those patients in whom surgical reconstruction must be delayed. The most common condition is that which follows excision of a neoplasm. Most surgeons prefer to delay restoration until it is clear that the possibility of local recurrence has passed; but in this period of waiting the loss of part of the face will present cosmetic and functional difficulties of great importance from both the psychological and the economic view-point (Fig. 1). Cosmetic considerations, as for example in cases of loss of the nose, often make less demand upon the skill and patience of the prosthetist than do functional restorations, as in loss of a lip. The control of dribbling is always a difficult problem, but no effort can be too great if it succeeds in freeing the patient from a condition which is so distressing as to make normal life almost impossible (Fig. 2). A minor practical point is that the intelligent use of a removable lining of chamois leather may often produce a watertight junction between the skin and the appliance.

The third group is by far the largest and comprises those cases in which the success of surgery depends upon the use of an appliance either as a temporary or a permanent measure. It is here that complete co-operation between the dental surgeon and the surgeon produces its most effective results. Although fixation of the appliance will often be derived from the teeth, the area concerned may well be remote. Such fixation is applicable to three main areas—the nose, the premaxilla and lip and the mandibular region.

Syphilitic destruction of the nose is essentially a loss of the mucous lining and cartilaginous septal support. The former is made good by a new skin-lining carried upon a mould which is supported by an appliance fixed to the upper teeth. In common with all such appliances this must be simple, efficient and foolproof, for it has to be worn for many months until the new lining is stable. Even when this is achieved support of the nasal bridge line is necessary. Sometimes this is provided by a bone or cartilage graft but on other occasions a prosthesis is preferable (Fig. 3).

In the premaxillary area the conditions most commonly requiring prosthetic reconstruction as part of a surgical programme are those associated with cleft lips or cleft palates.

Surgical closure of a palatal defect is frequently possible, leaving only the correction of dental deficiencies to the prosthetist. In some cases, however, there is insufficient material available to enable the surgeon to construct both an efficient soft palate and an intact hard palate. Under these circumstances the well-known Gillies-Fry operation may be used to reconstruct a movable soft palate from all the available tissues. The anterior defect is closed by a prosthesis which also retains the soft palate in its correct position and allows it a sufficient range of movement to enable it to function as an oro-nasal valve. The correction of secondary deformities of bilateral cleft lip may also demand a prosthesis. The tendency is for these lips to be adherent to the premaxilla and to be retroposed in relation to the lower lip. If there is sufficient transverse length of lip a satisfactory cosmetic and functional result will be obtained by freeing the lip and applying a skin inlay (Fig. 4). The prosthesis can then support the lip in its correct position but this new position is not obtained by building forward the upward gingival extension of the denture over the whole area of the inlay (which is usually at least from 4|4) but only by providing a relatively sharp central prominence between 1|1.

Not all bilateral lip defects should be so treated. If there is insufficient material in the lip, freeing it from the premaxilla will still not allow it to be brought forward to its normal position. The Abbé operation of transferring part of the apparently redundant lower lip into the upper may then be the method of choice. The total oral circumference is more evenly distributed between both lips and at the same time a competent buccal sulcus can be created to allow the wearing of a satisfactory upper denture to disguise the associated dental deficiencies (Fig. 5).

A somewhat less common condition is occasionally encountered. Some part of the upper sulcus may be lost through injury or disease. It may well be justifiable to reconstruct this by a skin inlay whilst upper teeth are still present. Such an operation will not increase the patient's immediate comfort, but it will ensure that if the time should come when a complete upper denture must be worn, satisfactory retention will be available. Such a procedure presents no difficulties whilst good teeth remain in the maxilla but later when these are lost the problems of fixation and of dental retention are immeasurably greater.

It is in the mandibular area, however, that deformities from disease or maldevelopment are most frequently encountered. The choice of the best method of treatment will depend on many factors but the most important is the dental state.

When there are sound teeth in good occlusion much can be done to alter the faulty mandibular formation by the application of bone grafts (Fig. 6). No risks to the teeth are incurred and no appliances are needed.

In other cases there may be good teeth which, owing to the mandibular deformity, are in poor occlusion but which can, on the model, be replaced in good position with a corresponding improvement in appearance. This condition is often seen in prognathism and the treatment is obviously mandibular section. The Kostecka operation is but one of many procedures which can be used and it is not always necessarily the best. Actual resection of a prearranged wedge from the body of the mandible may often be preferable.

When some teeth posterior to the canines can be conserved and those more anteriorly placed are of little value, the most frequently useful method of reconstruction is by deepening the buccal sulcus with a skin inlay to enable the new prosthesis to restore both dental function and cosmetic appearance. Such an inlay if applied in the presence of sound incisor teeth may in some cases result in gradual exposure of the necks of these teeth to such an extent that they are ultimately lost and the choice of method should be influenced by this possibility.



(*a*) (*b*) (*c*)

FIG. 1.—An "interval" prosthesis for use after surgical excision of carcinoma of the lip. (*a*) Appearance after excision of growth. (*b*) The denture which derives retention from the floor of the nose. (*c*) The cosmetic prosthesis.



(*a*) (*b*) (*c*)

FIG. 2.—(*a*) After resection of carcinoma of cheek. (*b*) Prosthesis to control dribbling shown in open position. (*c*) The final surgical restoration.



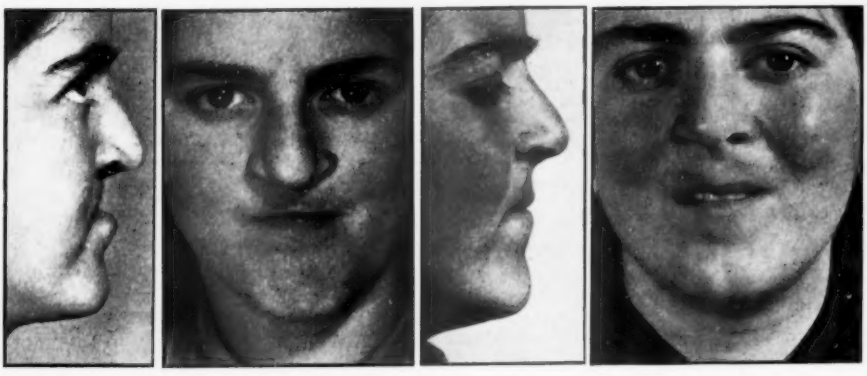
(*a*) (*b*) (*c*)

FIG. 3.—(*a*) Extensive specific destruction of the nasal lining and support. (*b*) Reconstruction by a skin lining followed by (*c*) a prosthesis which replaces the lost nasal skeleton.



(*a*) (*b*)

FIG. 4.—(*a*) Shows the retroposed position of a lip which contains sufficient tissue to enable it to be brought forward without tension. (*b*) The appearance after a skin inlay and the fitting of a prosthesis.



(*a*) (*b*) (*c*) (*d*)

FIG. 5.—(*a*) and (*b*) Show marked retroposition of the upper lip with shortage of tissue. (*c*) and (*d*) The completed result after the transposition of a full thickness wedge from the lower lip to the upper.



(*a*) (*b*) (*c*)

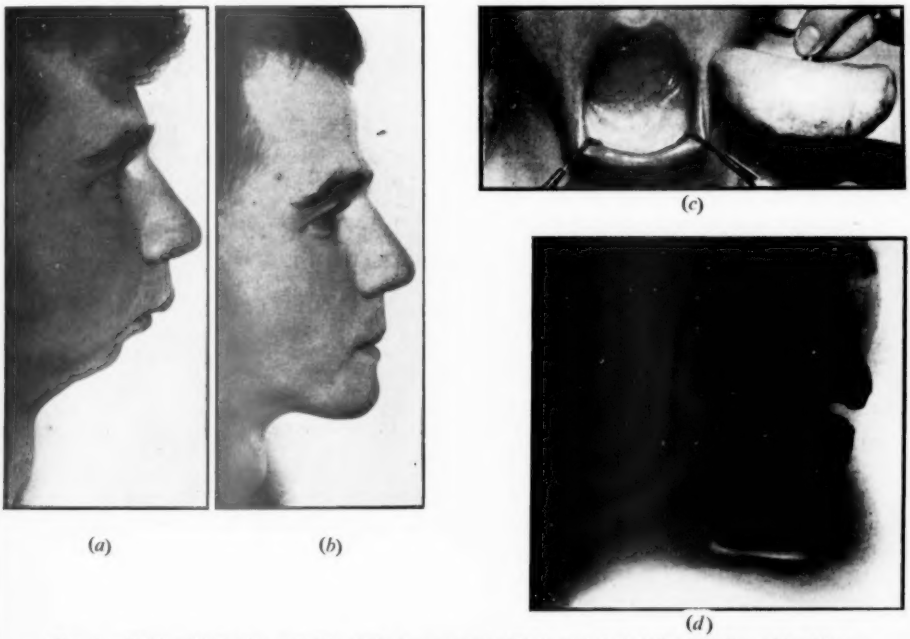
FIG. 6.—(*a*) and (*b*) Show the pre-operative and post-operative views of a correction of a minor degree of mandibular agenesis by bone-graft onlay. (*c*) Shows the graft about one year after insertion.

When no teeth can be conserved such a difficulty does not arise and the method of choice will most often consist in an inlay. This will allow scope for the creation of a denture which serves two functions (Fig. 7) (*see also Proc. R. Soc. Med.*, 1943, **37**, 7).

Lastly there is a group of cases in which the restoration of dental competence is the final phase of an extensive reconstruction. This type is well illustrated by those cases in which a bone graft has been used to restore mandibular continuity. Such an operation often fails to reconstitute the buccal sulcus. This may be restored on either the buccal or the lingual aspect by skin inlay to allow the new mandible to be used for its normal function of mastication.

It would seem, therefore, that there are few if any instances in which there is a marked bias in favour of surgical or of prosthetic reconstruction. Often enough they go hand in hand and success is dependent upon the choice of the most appropriate method of the particular problem. Very often, however, it is upon the skill of the prosthetist that the final result must be judged.

All the cases illustrated have been operated upon at the Plastic Surgery and Jaw Injuries Centre at St. Albans and I am indebted to my dental colleagues Mr. B. W. Fickling, Dr. A. B. MacGregor and Mr. P. Toller for their co-operation and skill in helping to provide these results.



(*a*) (*b*) (*c*) (*d*)

FIG. 7.—Bilateral infective arthritis of the temporomandibular joints in infancy followed by trismus and agenesis. (*a*) Pre-operative appearance. (*b*) Appearance after bilateral resection of the condylar remnants and inlay in the lower buccal sulcus. (*c*) The new skin-lined sulcus and the intermediate prosthesis. (*d*) X-ray to show the mandibular agenesis and the position of the prosthesis.

Professor Pomfret Kilner recalled that he had read a Paper before the Section on much the same subject in January 1947. He had dealt with it on slightly different lines but had covered most of the problems.

He strongly supported Mr. Mowlem's opinion that when the eye socket (orbital) region had been severely mutilated and the eye was missing, attempts to reconstruct new eyelids were ill-advised, for these must be immobile, and would serve only to hold in position a staring and necessarily disfiguring eye. In such cases, obliteration of the socket and the fitting of an external spectacle prosthesis was the treatment of choice.

It should be remembered that the angle-of-mouth acrylic hook attached to the upper teeth prevented stretching of the muscles of the cheek but left the paralysed half of the orbicularis oris to be stretched by movements of the other half of the face. It should therefore be considered only a very temporary measure.

The hinged prosthesis used to fill a cheek defect and minimize dribbling of saliva during the period of waiting for surgical repair was excellent. Anything which could render this waiting period less troublesome to the patient was to be encouraged.

Professor Kilner went on to say that everyone would agree about the importance of preserving teeth in those cases in which a prosthesis was worn in a skin-lined pocket in front of the mandible to camouflage underdevelopment or asymmetry of the mandible. Realizing that teeth might not always be available for the retention of a prosthesis and knowing that such a prosthesis often tended to tilt when attempts were made to bite on it, he—at the instigation of Mr. Greer Walker—had combined bone grafting with the epithelial inlay procedure. Bone chips were inserted, from a submental approach on the anterior surface of the mandible to build a shelf in this region. After a waiting period of three months the buccal inlay was carried out. He had reported a few successful cases to the Section three years ago and the Stoke Mandeville Unit now had several more cases in which this combination had given particularly pleasing results. It gave greater natural stability to the prosthesis which relied little or not at all on teeth for its retention. When bone alone was being used to build forward the chin region great care should be taken in the placing of this in correct position. There was a very marked tendency in such cases to build downwards, instead of forwards.

Some authorities had spoken adversely about the use of the nasal skin-graft pocket procedure—one of Sir Harold Gillies' greatest contributions—in the treatment of luetic deformity of the nose and of other forms of dish-face deformity. They argued that the cavity crusted and became offensive and was difficult to keep clean. This had not been his experience and he was glad to find that Mr. Mowlem advocated its use. The treatment of these cases was not finished until the nasal part of the prosthesis had been discarded and an intrinsic nasal bridge and tip support had been provided by a hinged or L-shaped cartilage graft. In earlier cases he used auto-grafts but in recent times preserved bovine cartilage had given most satisfactory results.

Mr. J. P. Reidy: In his remarks on facial palsy, Mr. Mowlem showed a slide where the paralysed face was supported during recovery by the insertion of a suitably shaped buccal prosthesis. I would like to know how soon this prosthesis is inserted and for how long it is worn. It is the practice at Stoke Mandeville in cases of facial palsy, whether likely to recover or not, to support the paralysed cheek by a fascia-lata sling, thus preventing over-stretching of the injured muscle. We are prepared to do this as early as two months from the onset of the lesion.

Mr. Mowlem also showed a slide depicting a large prosthesis filling a surgical defect in a patient's cheek, thus preventing the dribbling of saliva, which makes life so unpleasant for such patients. This appears to me to be a very excellent way of diminishing the misery which these patients have by reason of the fistula. However, I would ask Mr. Mowlem whether in the very old cases he would not proceed directly by surgery to close the cheek defect, as these older cases are likely to have a shorter lease of life and the risk of recurrence is not, in my view, as great as in younger patients.

Following total excision of the maxilla, I have no doubts in my mind that at present an epithelial inlay plus a prosthesis provide the most satisfactory means of restoring cheek contour. Has Mr. Mowlem any other ideas on this subject, because I remember a paper read three years ago in America in which a reconstruction of the maxilla by suitable skin and bone grafts looked promising?

In the treatment of the luetic nose the usual practice has been a nasal epithelial inlay with a prosthesis fitted to the upper denture to give bridge-support to the nose and to restore the general contour of the face. This is usually followed by discarding the prosthesis at a later date and inserting a graft along the nasal bridge. Mr. Mowlem uses bone for this purpose. On the other hand, whereas we used autogenous cartilage for that purpose, we now use ox-cartilage, the results of which have been promising.

Mr. Patrick Clarkson wished particularly to stress the value of a bilateral osteotomy of the ascending ramus of the mandible (Kostecka type) in a number of cases of open bite. Both for cases following fractures of upper and lower jaws and those seen in old cases of cleft lip and palate, particularly double cleft lip in which open bite is combined with a considerable degree of prognathism, the Kostecka operation was the simplest means of providing a reasonable occlusion and correcting the deformity of facial contour. If, after the Kostecka operation, gagging was to be avoided, it was essential that intermaxillary immobilization in cast-metal splints be prolonged for at least ten to twelve weeks and sometimes longer. He was sure that the bilateral osteotomy with "a slide back" of the jaw was a better operation in many cases of cleft lips than "masking operations" such as an epithelial inlay under the upper lip.

Mr. Clarkson also agreed with Mr. J. P. Reidy that the best late result in cases of syphilitic nasal deformity, treated by the Gillies' inlay operation, was sometimes only obtained by a late insertion of a strut of cartilage or bone along the bridge line, combined with closure of the oro-nasal fistula. This bone or cartilage graft was only possible after the patient had had the inlay and worn the prosthesis for a number of years. But if the graft could be done it gave the patient a good appearance independent of the prosthesis, and freedom from disagreeable consequences of a permanent oro-nasal fistula. The first of two cases for whom he had done this had had the inlay performed ten years before by Sir Harold Gillies who had referred the patient to him with the recommendation that a bone graft be done and the fistula closed.

Mr. Mowlem replied to both Professor Kilner and Mr. Reidy that the type of prosthesis used for support of a facial palsy at the St. Albans Unit does not have a hook at the angle of the mouth, so that stretching of the paralysed half of the orbicularis is unlikely. This support is applied as soon as the diagnosis is made or as soon as the patient is referred for treatment. With regard to the prosthesis used to control the dribbling of saliva, it is obvious that the indications for such an appliance are not very common. If the immediate surgical repair can be carried out this is done, but if there is any uncertainty that complete elimination of the original neoplasm has been achieved, the appliance is worn for from six to twelve months to carry the patient through the phase of immediate risk of recurrence.

Eosinophilic Granuloma

By D. Greer Walker, M.A., M.B., Ch.B., M.Dent.Sc.
and R. B. Lucas, M.D., M.R.C.P., D.P.H.

A destructive lesion occurring in bone has been variously described as solitary granuloma (Otoni and Ehrlich, 1940), eosinophilic granuloma (Lichtenstein and Jaffe, 1940), or non-specific granuloma (Hill, 1949). The lesions may be single or multiple, involving no particular bone or site in a bone (Engelbreth-Holm *et al.*, 1944).

There has been much controversy as to the exact nature of this lesion, some preferring to describe it as a separate entity and attributing it possibly to trauma or to some inflammatory lesion of the bone, while others have taken the view which might best be summed up in the words of Farber (1941) that this benign, destructive lesion does not constitute a new disease. It represents, rather, one variant of a basic disease process of which the clinical pictures known as Hand-Schüller-Christian disease, certain forms of xanthoma, and Litterer-Siwe disease are other examples. This latter view seems to be more generally accepted, but the division of opinion shows how little is known of the exact nature of this condition.

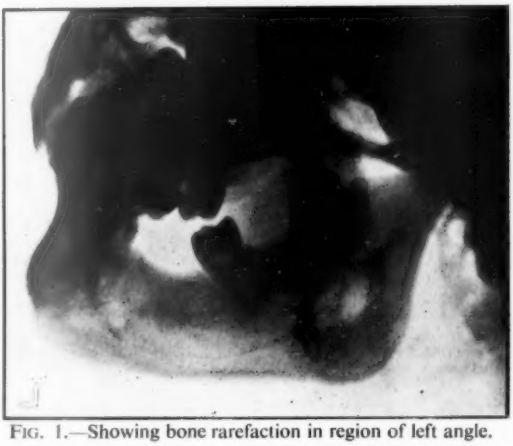


Fig. 1.—Showing bone rarefaction in region of left angle.

There are, however, one or two well-established points. The disease appears either to be symptomless or to exhibit manifestations of a very minor degree, the commonest complaints being of slight pain and swelling, with occasional general malaise. The sites of the lesions present no particular pattern. The solitary lesion is more prevalent than those cases with multiple lesions. Blood and urinary examinations reveal little apart from the slight eosinophilia, as mentioned by some authorities. Males are more commonly affected.

It is fortunate that the treatment of this obscure condition is simple. The lesion responds very well to radiotherapy, and many cases have been treated successfully on these lines. There are others who prefer surgical treatment, where curettage will be found equally successful.

Case Report

J. W. A., male, aged 27.

History.—About one month previously he was complaining of a slight, dull ache in the left angle of the lower jaw. The dental surgeon, unable to find a cause for the pain, referred him to Mr. D. R. Curnock, who also thought there was no lesion of the teeth to account for his symptoms. There was very little swelling to be seen but it had caused a small degree of trismus. There was only one remaining lower molar near the lesion, and this tooth was healthy. A radiograph of the left angle (Fig. 1) showed a lesion present which was reported on by Dr. Campbell Golding as follows:

"There is some bone rarefaction in the region of the left angle of the mandible. It has little, however, in the way of specific appearances. There are no obvious diagnostic features."

On February 16, 1948, the patient was admitted to Stoke Mandeville Hospital. It was decided to perform a biopsy. This proved the lesion to be an eosinophilic granuloma. At the same time as the biopsy was performed it was thought wise to do a débridement of the area.

Microscopical examination of the granulomatous-like tissue thus obtained showed that there had been replacement of the bone of the affected area by a cellular mass (Fig. 2). Under the higher powers three main types of cell were seen (Fig. 3). Most prominent were the eosinophils, which were present in large numbers and appeared to be similar to the eosinophil leucocytes of the blood: cells containing coarse oxyphilic granules and with, usually, a bilobed nucleus. Also present in quite large numbers were foam cells—tissue histiocytes which had taken in lipoid material, producing a foamy, reticulated appearance of the cytoplasm. Numbers of large, multinucleated giant cells were prominent. These were of the foreign-body type, containing up to 20 or 30 nuclei irregularly disposed throughout the cell body. In addition, lymphocytes, neutrophil leucocytes and occasional plasma cells were also present.

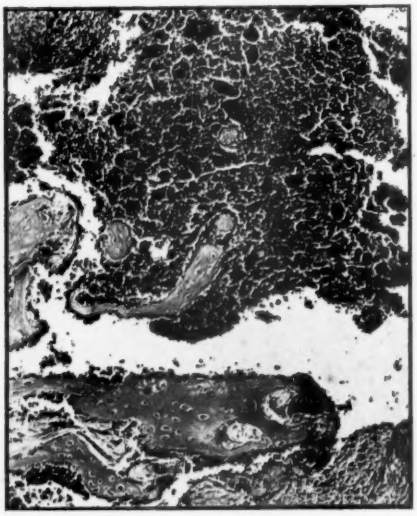


FIG. 2.—Showing replacement of bone by cellular infiltration. × 83.

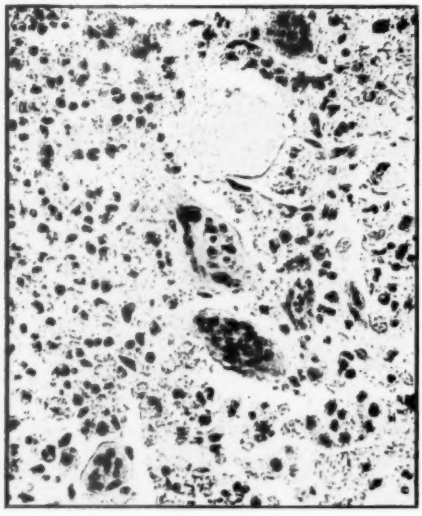


FIG. 3.—Detail from Fig. 2. × 360.

X-ray examination of the chest, pelvis, long bones and skull revealed no abnormality. Complete blood analysis, including calcium, cholesterol and blood sugar, were all within normal limits.

Follow-up.—When seen one month ago it was noted that there was no recurrence or development of any other lesion clinically. Dr. Campbell Golding's last X-ray report in January 1950 stated: "The affected area has resolved to some extent and is about half its previous size."

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Section of Obstetrics and Gynæcology

President—LESLIE WILLIAMS, M.D., M.S., F.R.C.S., F.R.C.O.G.

[*March* 17, 1950]

DISCUSSION ON THE USE OF ŒSTROGEN THERAPY IN GYNÆCOLOGY

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Études sur la pseudo-gestation et l'œstrus prolongé après injection de fortes doses d'œstradiol chez la rate adulte

RÉSUMÉ.—Tous les animaux ont été examinés à des moments différents au cours des trois semaines qui suivirent les injections.

L'originalité de cet article consiste dans le fait que des transformations endométriales ont été observées au cours de la phase pseudo-gestative bien connue. Cette phase suit immédiatement les injections. Ensuite la muqueuse utérine reprend son aspect œstral ou diœstral. Des faits similaires, mais moins accentués, ont été observés dans les mêmes conditions chez des animaux castrés.

L'œstrus continu, qui succède immédiatement aux transformations de pseudo-gestation de la muqueuse vaginale, est caractérisé par la croissance d'un grand nombre de follicules jeunes et par la maturation kystique de certains autres. La membrane folliculaire de certains peut se plisser. Ceci a une cause ovarienne.

Il faut remarquer également les stades intermédiaires qui apparaissent entre ces deux phases dans le vagin.

Quatre animaux ont eu une hémorragie du type post-œstral dans la lumière vaginale.

Studies on Pseudogestation and Prolonged Œstrus after Injection of Large Doses of Œstradiol in Adult Rats

Summary.—All the animals were examined at different times during the three weeks that followed the injections.

The originality of this paper consists in the observation of endometrial retrogressive transformations during the well-known pseudo-pregnant phase.

This phase immediately follows the injections and at its end the uterine mucous membrane resumes its œstrous or diœstrous state. Similar, but less marked, appearances have been noticed in the same conditions in castrated animals.

The continued œstrus, that immediately follows the changes of pseudo-pregnancy in the vaginal mucosa, is characterized by the growth of a greater number of young follicles and the cystic maturation of some others: the follicular wall of some of them can become wrinkled. This has an ovarian cause.

Intermediate states also appeared between those two phases in the vagina.

Four animals had hæmorrhage in the vaginal lumen; the hæmorrhage was of a post-œstrous type.

INTRODUCTION

This article is written with a view to presenting the effects of injections of large doses of œstradiol on the ovaries and the genital tract.

Although the luteinization obtained in the ovaries after injections of variable quantities of œstradiol is well known through the published researches of Scaglione (1930), Hohlweg and Junkmann (1932), Hohlweg (1934), Hohlweg and Chamorro (1937), Desclin (1935), and Bourg and Spehl (1948), literature on the development of this luteinization and on

the further modifications which might take place in the ovaries before their return to normal is very limited.

Only Merckel and Nelson (1940) have studied in a series of adult female rats the subsequent results of a single injection of 400 R.U.

In presenting the interpretation and discussion of the results we have obtained, a comparison will be made between the established facts and those we have noticed.

These experiments were made for the same purpose as those of Greene and Burrill (1941)—by injection of one large dose of œstradiol propionate at birth and further permanent œstrus; of Turner (1941) by injection of 100 or 200 I.U. of œstrogen during the first ten days of life and later observation of the prolonged œstrus period; and of Hale (1944)—superimposable results obtained with diethylstilbœstrol provided that the injections are made during the first fourteen days.

Although the experiments here reviewed are based upon reduced periods of observation of the injected animals, they have the advantage of determining the transition from the pseudo-pregnant phase to the persisting œstrous phase, thus permitting the precise determination of the ovarian mechanism provoking the reactions of the genital tract.

From a general biological point of view, we regard it more and more necessary, not to estimate the immediate action of single or combined hormone injections, which is already well known, but to try to measure the continuance of this action and the multiple and prolonged effects that it could have, not only on the receptor itself, but on the whole endocrine system with a possible selective effect on certain individual glands.

Our experiments consisted in injecting 42 adult female rats with a routine total dose of 2·25 mg. of œstradiol, at a rate of 0·25 mg. every day or every other day.

The animals were killed after periods of time varying from five to twenty-one days after the injections ended. We ignored the phase of the cycle in which the injections were commenced.

During these experiments, only the histological alterations met with in the genital tract were studied. The ovaries were cut serially and stained with Masson's trichrome or with hæmalum-eosin. The uterine horns and the vaginas were cut at various levels. It was deemed necessary to examine a series of animals previously castrated and injected in the same way as the others, to be able to interpret, at least partially, the reactions we observed in the genital tract.

The results are condensed in three tables, according to the state of the vaginal mucous membrane: Table I relates to animals of which the vaginas were in pseudo-pregnancy; Table II to those which were in œstrus or diœstrus; Table III concerns castrated animals.

Study of the Ovaries and Genital Tracts of Animals with Vagina in Pseudo-pregnant State

Ovaries.—All female rats, in whom the vagina displayed mucoid transformation of the superficial layer, had recent corpora lutea in their ovaries. The clear histological appearance of the latter is due to voluminous lutein cells of functional aspect. These corpora lutea neither display retrogressive cellular signs of cytoplasmic vacuolization, nor regression in size of the constituent elements, nor pyknosis of nuclei (Figs. 1, 2, 3).

They can be watched up to the sixteenth day after the end of injections. Old corpora lutea are rare. False cystic corpora lutea are frequently found: their granulosa degenerates quickly and their theca, undergoing a progressive discoid thickening, luteinizes. (Fig. 1). Those elements are usually not very numerous and generally smaller than the full corpora lutea, which are about the same size as the normal gestative corpora lutea of a female rat.

These elements, however, progressively acquire a mature appearance (Fig. 3) and it is then no longer possible to distinguish them from the others by their histological appearance. The growth of the normal follicles is slight; it particularly involves small and medium-sized elements (Fig. 2); bigger elements than the mature follicles are only met with exceptionally. The interstitial tissue of the ovary is hardly more developed than normally and it may be almost completely missing.

Uterus.—The uterine horns are often dilated and contain a whitish or aqueous fluid under pressure. The most peculiar reaction is a considerable leucocytic infiltration that can be noted from the fifth to the twelfth day. Numerous clumps of pseudo-eosinophilic leucocytes originate from the thick muscular layers and infiltrate the chorion diffusely (Fig. 14). A true leucocytic accumulation, with the appearance of miliary abscesses, occurs in the dilated glands; this accumulation progressively destroys the epithelial lining (Fig. 11). Sometimes

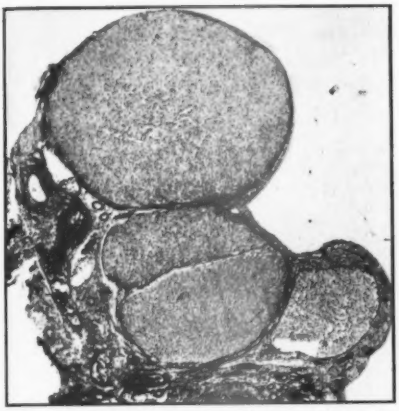


FIG. 1.—Pseudopregnant c.l., excentric cystic false c.l., single cystic atresia. R8 eighth day after injection of 2·25 mg. of benzoate œstradiol in ten days.
c.l. = corpora lutea (throughout).

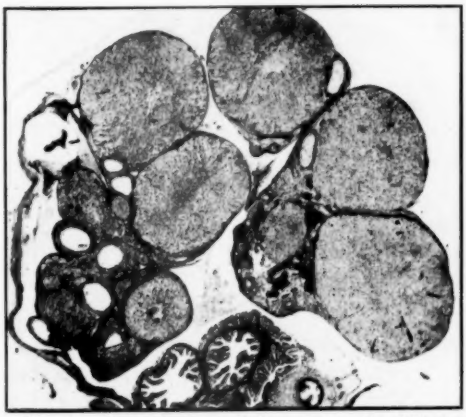


FIG. 2.—General aspect of the ovary on the fifth day after cessation of injections. Note c.l. of pseudopregnant appearance in moderate number, 5 are cut at the maximum of their dimensions, 2 at the edge. Note appearance of medium-sized follicles. R25. Obj. 1.

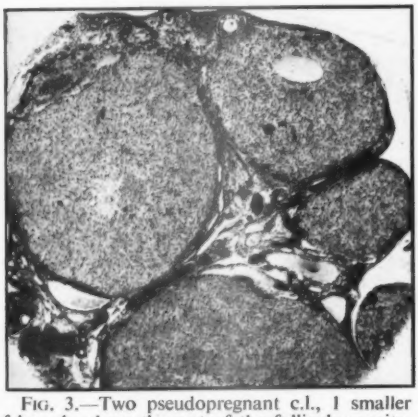


FIG. 3.—Two pseudopregnant c.l., 1 smaller false c.l. where the rest of the follicular cavity, with oval and regular outlines, persists. R25 fifth day after injections. Same enlargement.



FIG. 4.—Different stages of retrogression of c.l.: small false c.l. with residue of the cavity. Intense growth of small follicles. Marked vascular congestion. R3 twenty-first day after.

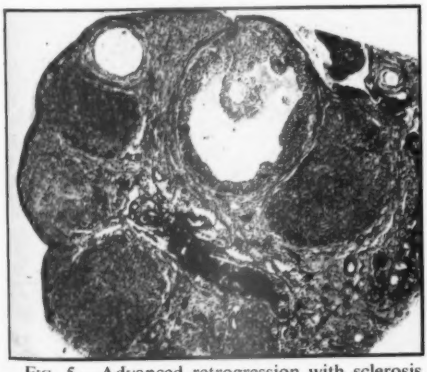


FIG. 5.—Advanced retrogression with sclerosis of the c.l. Wrinkled large follicles containing the ovocyte. R14 twentieth day after injections.



FIG. 6.—Same enlargement as Fig. 2. Sixteenth day after. C.l. in sclerotic retrogression, with large follicles, and one false cystic c.l. sixteen days after end of injections.

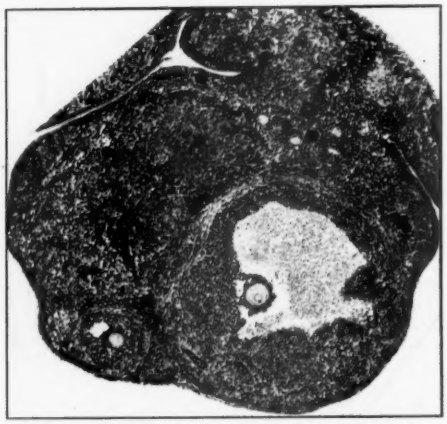


FIG. 7.—Strongly marked wrinkled follicles containing the ovocyte; old c.l.; below: medium-sized follicle. R14b twentieth day after injections. Obj. 3.



FIG. 8.—Vaginal mucified mucous membrane on the fifth day after injections. See same animal's ovary Fig. 2. Note narrowness of basal layer and two small mucous cysts. R25. Obj. 5.

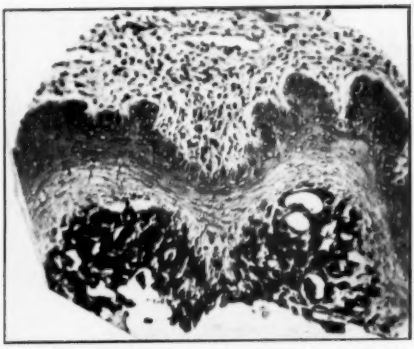


FIG. 9.—Development of œstrus beneath the mucified epithelium. Fifth day after injections. R7. Obj. 5.

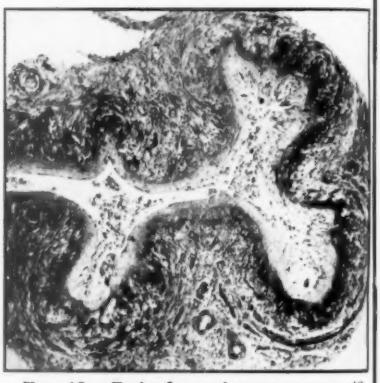


FIG. 10.—End of pseudopregnant mucification. Fifth day after injections. Œstrus beginning. R24. Obj. 3.

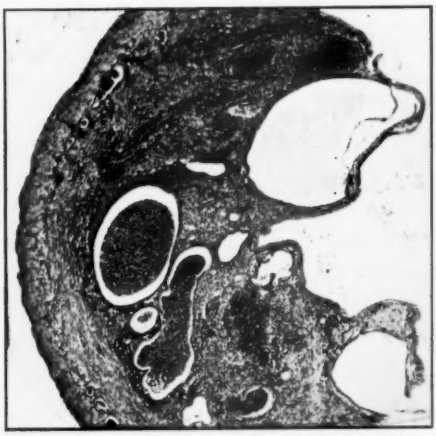


FIG. 11.—Polynuclear infiltration simulating miliary abscess in dilated glands. Big cystic subepithelial dilatations. Miliary abscess of the chorion. R5 fifth day after injections. Obj. 2.

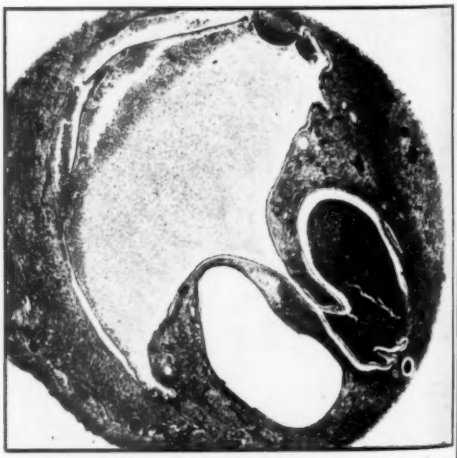


FIG. 12.—The same. Note hydropyometria and, on the right-hand side, small miliary abscess having broken through the epithelium. R PY 1 seventh day after injections. Obj. 2.

a miliary abscess is formed under the lining epithelium; it may break the latter and diffuse into the uterine cavity itself (Fig. 12).

The epithelium of the superficial layer undergoes a considerable change: true polypoid structures develop, consisting of papillæ covered with epithelial cells that are often tightly packed. These vegetations progressively form pedicles; at the same time colour changes appear denoting cytological alterations (Figs. 13–15). Soon after, a healthy unicellular epithelium progressively constricts the pedicle and fragments of endometrium are shed (Fig. 13). This process is observed from the fifth to the twelfth day. The animals having passed through this stage which corresponds with the shedding of fragments of mucosa, then show a unicellular epithelium that sometimes resembles the œstral epithelium, or in some other cases like the epithelium coating the oviduct in the course of the normal cycle; cells of the intercalated type are particularly noted there. At the end of this process, the endometrium has again a diœstrous aspect and the glands are shrunken and small, though a rather profuse leucocytal infiltration may persist.

It should be noted that different, more or less advanced, changes may be found in the same animal at different levels in the uterine horns.

The endometrial alterations do not develop everywhere simultaneously. This is perhaps the reason why the retrogressive endometrial changes may have so far passed unnoticed.

We have not looked to see whether these alterations undergo an acceleration, from the bottom of the uterine horns to the top of them or inversely.

Vagina.—The pseudo-pregnant aspect may be complete and the thin basal layers are then lined with several cellular layers, elements of which sometimes contain an abundant mucous secretion, forming large cystic vacuoles (Fig. 8).

The squamous appearance of deep layers corresponding to a distinctive œstrus development (Fig. 9) and sometimes the almost total desquamation of the mucous layers are noted in some animals (Fig. 10) at the end of pseudo-pregnant phase and already observed on and after the fifteenth day, indicating that the pseudo-pregnant state is directly followed by true œstrus.

There is no connexion between the duration of the pseudo-pregnant phase and the fact that the animals have been injected with the total amount of œstradiol in ten or twenty days. The vagina of 4 animals out of 16 contained a little hæmorrhage.

Study of Ovaries and Genital Tracts of Animals with Vagina in Œstrus or Diœstrus

General study.—This series include 11 animals studied over a period from the seventh to the twenty-first day after the end of the injections.

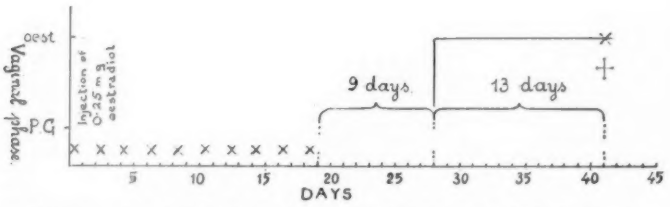


Diagram of evolution of pseudogestational phase—19th–28th day—and prolonged œstrus—28th–41st day—as shown by vaginal smears. R3.

That would by no means imply that the œstrus continues over such a long period, as consideration was not given in each animal to the varying factor of the end of the pseudo-pregnant reaction in the vaginal mucous epithelium, and it was noticed that this appears from the seventh to the sixteenth day after the end of the injections. But examination was made, by means of daily vaginal smears, of a certain number of animals, namely R1, R14, R3 and R4. In these, the œstrus started on the eighth or ninth day after the last injection, remained constant and uniform and stopped for R3 and R4 on the twenty-first day. This proves that a prolonged period of continuous œstrus arises, the extreme limit of which has not been exactly determined. The longest period that we studied lasted thirteen days.

Ovaries.—The size of this organ is often notably reduced and some animals showed extremely small ovaries, the largest sections of which measured 3×2 mm. although in the course of full development of the pseudo-pregnant phase, they may measure 5·5×3·5 mm.

The corpora lutea in involution are generally not very numerous; the regressive process of corpora lutea seems to be short-lived. False corpora lutea are nearly always absent except on the twentieth and twenty-first days when extensive follicular formation appears; their theca shows commencing localized luteinization (Fig. 6).

On the other hand, an intense follicular growth is noted; it is characterized by the display of a large number of young subcortical follicles (Fig. 4).

The medium-sized follicles show no peculiarity, but follicles of abnormal dimensions, equal to or bigger than those of corpora lutea, yet with a cystic aspect, appear in almost all the ovaries (Fig. 6). Some of these elements, present particularly about the twentieth day, assume a wrinkled shape, which in rats, is distinctive of incompletely ruptured follicles (Figs. 5–7).

The interstitial tissue grows in size most markedly from the seventh to the twentieth day.

Uterus.—The size of the uterine horns diminishes progressively; hydrops is an exception; the muscular layers are always hypertrophic. Retrogressive endometrial changes can be noted up to the seventh day. When they are over, the epithelium takes on an œstral appearance that progressively leads to rest.

Only moderate dilatation of the glands was noted, even in the animals which underwent the longest œstral period; the leucocytic infiltration ends together with retrogressive endometrial transformations. With the regeneration of the new endometrium, it can be noted that the mucous membrane divides in two distinctive zones: the internal one in which the chorion has a cellular look (cytogenic chorion), the deeper of the two, and the external one very poor in glands and formed of a collagenous chorion. When leucocytic infiltration persists it is only noted in the first zone.

Vagina.—In 4 animals, the vaginal lumen contained blood mixed with desquamated keratinized cells, isolated or in patches (Fig. 18).

Supplementary note.—Two animals were in diœstrus on the sixteenth day. The histological investigation of their ovaries was characterized by numerous old corpora lutea and rare false corpora lutea. Their follicular aspect was not different from that of animals still in œstrus. The uterus was of reduced size and at rest. The glands alone retained some cystic appearance.

Study of the Genital Tracts of Castrated Animals Injected Under the Same Conditions

These results cover a series of 14 animals; they were all injected with the same total quantity of 2·25 mg. in ten days and were examined during the sixteen days that followed.

None of these animals showed any pseudo-pregnant mucous reaction of the vagina. Œstrus stopped on the eighth day (Fig. 17); the decline of this process with recurrence to diœstrus could be noted down to the sixteenth day.

In 2 animals, the vaginal lumen contained blood on the fifth day.

As for the uterus, the hydrops gradually regressed and was no longer met with after the twelfth day. Some aspects of regressive epithelial alterations, with large leucocytic infiltration, were noted from the fifth to the eighth day. They appeared together with a striking subepithelial vascular congestion that gave the preparations a distinctive appearance (Fig. 16). From the twelfth day, the epithelium was constantly in diœstrus. Subsequently, a differentiation of the chorion was noted, into an internal part of clear appearance (cytogenic chorion) and an external part made of darker cells with collagenous aspects, as happens with non-castrated animals.

Interpretation and Discussion

The mucous pseudo-pregnant reaction, noted in the vagina after the injection of a large dose of œstradiol, is well known (Merckel and Nelson 1940; Bourg and Spehl, 1948). It is obvious that this reaction is dependent on the very large corpora lutea which, although reduced in number, fill almost the whole of the ovarian parenchyma (Desclin, 1947, 1949).

Our experiments were not unlike those of Merckel and Nelson, who injected adult female rats with a single dose of 400–500 R.U. After a diœstrus interval of fifteen to seventeen days, due to pseudo-pregnancy, those animals showed one or two spontaneous cycles and then passed through a period of rest of about ten days. These authors also noted a continuous



FIG. 13.—Polypoid formations in process of necrosis, progressively separated from their base by healthy epithelium of clear aspect and consisting of a single layer of cells. Obj. 3.



FIG. 14.—Leucocytic trails emanating from muscular layer and diffusely infiltrating the chorion. R PY 2 seventh day. Obj. 5.



FIG. 15.—Retrogressive endometrial process and polypoid formations, with persistent hydrops. Uterus at R7 fifth day after end of injections. Obj. 1.

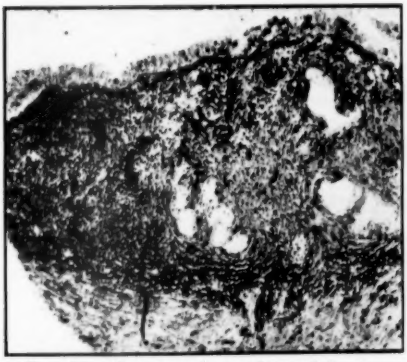


FIG. 16.—Retrogressive endometrial process in castrated female rat (fifth day). Note big subepithelial vascular congestion with blood suffusion. Glands still moderately dilated. R18c. Obj. 3.



FIG. 17.—Vagina of the same animal, still in œstrus, with blood mixed with desquamated keratinized layers. R18c. Obj. 1.

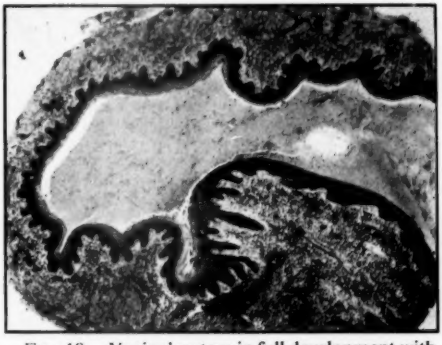


FIG. 18.—Vaginal œstrus in full development with blood mixed with keratinized cells in the lumen. RT3 seventh day after.

The illustrations show the results of œstradiol injections in adult rats.

œstrus, after pseudo-pregnancy, in animals injected daily with 40 R.U. during the whole experiments. They ascribed this prolonged œstrus to the cessation of functional activity of corpora lutea and to the direct action of the injected hormone on the vagina. Our experiments are complementary to those of Merckel and Nelson, since ours investigate the evolution of ovarian and utero-vaginal reactions subsequent to the end of injection of œstradiol-benzoate, prolonged for ten or twenty days; moreover, they allow the interpretation of the reactions we noted in the genital tract, as they included a series of castrated animals injected under the same conditions.

The quantities injected being greater, the resulting reactions proved much more accentuated and allowed the observation of new facts and perhaps also the more accurate interpretation of the results we achieved.

First of all, the duration of the pseudo-pregnant period, in which the corpora lutea remain functionally active, extends up to the sixteenth day and therefore does not seem to be influenced by the variants resulting from our own experiments. It may disappear as early as the seventh day and be immediately followed by œstrus.

Merckel and Nelson have shown that the persistence of pseudo-pregnancy can be obtained only with animals injected in œstrus, and that it is noted only in 3:10 of the animals injected in diœstrus.

The large doses injected are probably responsible for the constancy of the pseudo-pregnant state during the first five days that follow, for we did not consider the phase of the cycle in deciding when injections were to begin.

In the majority of the ovaries examined during this stage, it was possible to demonstrate false corpora lutea of thecal origin with cavities more or less cystic or merely persistent. Those elements can be superimposed on those obtained with the same animals by injecting urine from a pregnant woman or prolactin (Desclin, 1947, 1949). According to this author, the prolactin might contain traces of L.H. (luteinizing hormone) which are responsible for these changes.

The fact that such marked luteinization of the ovary does not prevent follicular development is to be emphasized.

In the uterus, the endometrial reactions, noted *at the end of the injections*, are characterized by a striking thickening, an increase in size of the cells of the epithelium and above all of those which line the glands. The appearance of the latter becomes superimposable on that of the epithelium itself; we termed this fact and its appearance "glandular epithelization" (Bourg and Spehl, 1948). It should be noted that the glands become cystic.

The alterations we observed there *after the end of the injections* are mainly retrogressive; they are characterized by real interchorial or interglandular leucocytic accumulations destroying the epithelial lining—like miliary abscesses—and by the condensation of endometrial fragments, which readily assume a polypoid appearance, necrose and desquamate with the progressive reduction of their pedicles. This reduction results from a growth of a new epithelial bed at their base. We call this process "retrogressive endometrial transformation." It is to be noted that this transformation, with some variants, looks like the desquamation of the functional layers of the human endometrium in the course of menstruation; it also resembles the necroses of the superficial layers of a female cat's endometrium, that has been noted in the course of the post-luteinic phase experimentally induced (Bourg, 1933, 1935). These "retrogressive endometrial transformations" are also noted in castrated animals during the first eight days that follow the injections of the same dose of œstradiol. They merely present a more pronounced character in non-castrated animals. Therefore, the influence of the ovary does not extend to the quality of this reaction but solely to its intensity.

How may the prolonged œstrus, that follows pseudo-pregnancy, be interpreted? According to Merckel and Nelson, it ensues from the direct action of several injections of œstradiol, as indeed they have not observed this effect after injecting only one dose of this hormone.

This is what we have noted: As soon as the injections are over, the castrated animals have a permanent œstrus, which may last twelve days. This can merely result from the prolonged effect of large doses injected into the vaginal mucous membrane. In our opinion, however, it would be worth carrying out further experiments.

Such a type of œstrus is not to be compared with the one which occurs only on the eighth to ninth day after stopping injections and may continue up to the twenty-first day and probably even beyond in non-castrated animals.

Now, the examination of the ovaries at that stage shows an obvious histological retrogression of the corpora lutea and an intense follicular growth, quite distinctive and already foreseen by Merckel and Nelson; this has, no doubt, been increased in our experiments,

owing to the intensity of the induced reactions. It results in the formation of voluminous cystic follicles and of wrinkled atretic follicles which look like the normal follicles just at the end of maturation described by Long and Evans (1922).

The cystic follicles may show the beginning of luteinization of the theca.

It is to be noted also that the interstitial tissue of the ovary undergoes simultaneous growth.

Thus the prolonged œstrus must be attributed to œstrogenic ovarian secretions probably localized in the follicles and interstitial cells. This second reactive phase occurs several days after the injections of œstradiol benzoate have stopped.

The uterine reactions of this prolonged œstrus are only slightly accentuated; they are not very different from the normal cyclical œstral aspect.

It is plain that the ovarian alterations, brought about in these experiments by injections of œstradiol in adult female normal rats, are consequent upon reactions started perhaps in several other endocrine glands, but certainly in the anterior hypophysis (Hohlweg and Chamorro, 1937; Desclin, 1935; Merckel and Nelson, 1940; Selye, Collip and Thomson, 1935). Hitherto, all authors admit a prevailing and almost exclusive secretion of L.H.

We think that these reactions of the hypophysis vary according to the injected dose and that, with a large dose of 2·25 mg. in ten or twenty days, pseudogestative functional corpora lutea result from the action of the luteotrophic principle described by Astwood (1939, 1941) and not yet well known; false atretic corpora lutea result probably from a new and persisting secretion of L.H. (luteinizing hormone). Of course, they are new formations of a luteinized type and can nearly be observed, more or less numerous, at any moment of these experiments; but during the pseudogestative phase the F.S.H. (follicle stimulating hormone) secretion is not completely inhibited or rather it may be also slightly stimulated. As soon as the secretion of luteotrophic hormone decreases, the secretion of F.S.H. increases and exceeds the normal one.

That is how we can explain the considerable follicular growth, noted from the seventh to the twenty-first day, and formation of cystic or wrinkled follicles and, as a consequence of these reactions, the prolonged œstrus.

It is, therefore, considered that the hypophyseal reactions, continuing after the end of the injections and following each other in a definite rhythm, are, through the changes in the ovaries, the initiators of this prolonged œstrus, subsequent to the pseudo-pregnant phase.

As for the presence of blood in the vaginal lumen, it was encountered during the pseudo-pregnant phase as well as in the course of the subsequent œstrus, and in castrated animals in œstrus too. In 6 out of 9 cases it corresponds with the phase of retrogressive endometrial change; it can be explained by the intense congestion that usually accompanies this process; the fact of not having noticed its presence in the endometrium does not prove that slight hæmorrhage or blood-stained exudation does not occur at this level; indeed, either the shed blood may be eliminated from the uterine cavity during histological processes or it may quickly disappear from this part of the genital tract.

Conclusions

(1) Changes in the ovaries and in the genital tract are caused by doses of 2·25 mg. of œstradiol-benzoate injected daily for ten or twenty days into adult female rats. These changes go on for at least three weeks after the injections have been stopped.

(2) Two kinds of reactions are observed in the ovaries; first the pseudo-pregnant and functional corpora lutea persist during a variable period of five to eighteen days; later an intense increase of follicular activity occurs which may begin as early as the seventh day and go on till the twenty-first day. It leads to the formation of cystic follicles and wrinkled follicles.

(3) The vaginal reactions which we observed are parallel with the ovarian changes: a mucoidal transformation of the superficial layers of the mucous membrane corresponds with the period of luteinization; continued œstrus corresponds with the intense follicular change.

(4) In each period of ovarian change, the formation of false corpora lutea can be noted at different stages. The early stages are characteristic of the last days during which the observations have been made (twentieth and twenty-first day).

TABLE I.—MUCIFICATION
(PSEUDO-GESTATIONAL PHASE)

Number	Number of days	Vagina	Ovaries							Uterus		
			Recent corp. lut.	Old corp. lut.	False corp. lut.	Small follicles	Medium follicles	Interstitial	Cystic follicles	Epith.	Cystic glands	Leucocytic infiltration
R 5	5	++	+++	Rare	+	+	+	+	0	Hydr. œ.	G.C.H.	++++ miliary abscess
R 6	5	++	+++ type G	Rare	+	+++	+++	0	0	Hydr. œ.	0	++
R 7	5	+ end HH	+++ type G	Rare	++	+	+	0	0	Œ. R.E.P.	+	++++ miliary abscess
R23	5	++	+++ type G	0	+	+	++	0	0	Hydr.	±	0
R24	5	+ end	+	0	++	++	+	0	+	Hydr. R.E.P.	0	++
R25	5	++++	++++ type G	Rare	0	+	++	0	+	R.E.P. end pro-œ.	+	±
T 2	7	+ end	++ type G	Rare	+	++	+	0	0	R.E.P.	0	+++
PY1	7	+ end	++	0	0	++	+	++	0	R.E.P. Hydr.	0	+++
R 8	8	+ end	++	+++	++	+	+++	++	+	Œ + S.M. R.E.P.	+ S.M.	+
R 9	8	++	+++	0	0	+	++	0	±	Œ.	+ Epith.	±
R10	8	++ HH	+	++	++	+	++	0	0	Hydr. œ.	++	++
R11	8	+ end	++	0	+	+	++	0	0	Œ.	0	+
R 2	12	++ HH	+++	0	+	0	++	0	±	Œ.	++	++++ miliary abscess
R22	12	+ end	+++ type G	0	+	Rare	+	0	++	R.E.P. + end	0	+
R21	12	++ HH	+++	0	0	++	++	±	0	Diœ.	0	0
R19	16	++	++	+++	+	++	+	0	0	Diœ.	0	++

TABLE II.—ŒSTRUS

Number	Number of days	Vagina	Ovaries: Recent corp. lut.	Old corp. lut.	False corp. lut.	Small follicles	Medium follicles	Interstitial	Cystic follicles	Uterus: Epith.	Cystic glands	Leucocytic infiltration
T 1	7	++	0	+	++	+++	+++	++	0	R.E.P.*	±	++
T 3	7	++ HH	0	++	0	++	+	++	0	R.E.P. end	+	++
PY3	7	++	+	+	0	++	+	+++	++	Œ.	+	+
PY2	7	++ HH	0	+	0	++	+	+++	0	R.E.P. œ. Pyo. Met.	0	+++
R 1	12	++	0	+	0	+	+	+++	+	Diœ.	++	++
R17	16	+++	+	++	0	+	+	++	++	Œ.	+	++
R16	20	++	0	+	0	+++	+	++	++	Œ. Hydr.	0	0
R15	20	++	0	++	0	+++	+	+	+++	Œ.	0	0
R14	20	++ HH	++	+	±	+++	+	+	+++	Œ.	+	0
R 3	21	++	+++	+	+	++	++	+	++	Œ.	0	+
R 4	21	++	+	0	++ beginning	+++	+	++	+	Diœ.	0	+
DIŒSTRUS												
R20	16	Diœ.	+	++	+	+++	++	++	++	Diœ.	+	+
R18	16	Met→ diœ.	+	+++	+	++	++	0	+	0	+	±

* retrogressive endometrial process.

TABLE III.—CASTRATED ANIMALS

Number	Number of days	Vagina	Uterus				
			Hydrops	Epith.	R.E.P.*	Cystic glands	Leucocytic infiltration
14c	5	Œ.	++	Œ.	0	+	++
15c	5	Œ.	++	Œ.	0	+	++
18c	5	Œ. HH	+	Œ.	End.	+	+
19c	5	Œ. HH	++	Œ.	+	0	0
5c	8	Œ.	0	Œ.	0	+	+
6c	8	Œ.	+	Œ.	+	0	+++
17c	12	End. œ.	±	Œ.	+	+	+
20c	12	Œ.	±	Diœ.	0	±	±
7c	8	Œ. diœ.	0	Diœ.	++	++	++++
21c	12	End. œ.	0	Diœ.	0	+	0
11c	16	Diœ.	0	Diœ.	0	±	±
12c	16	End. œ.→ diœ.	0	Diœ.	0	±	++
13c	16	Diœ.	0	Diœ.	0	+	0

* retrogressive endometrial process.

CONCLUSIONS (*continued*)

(5) The endometrium undergoes retrogressive changes from the fifth to the twelfth day after the injections have been stopped. These changes are characterized by a leucocytic infiltration of multinodular appearance, an epithelial disintegration and a desquamation of polypoid fragments in process of lysis. Such changes, occurring also in castrated animals, result solely from cessation of the action of the large quantities of œstradiol administered.

(6) The presence of blood in the vaginal lumen is noted in some animals. This seems to be the result of the intense congestive processes occurring in the endometrium in the course of the changes it undergoes; it may therefore be considered the equivalent of a post-follicular hæmorrhage.

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Œstrogen Therapy in Relation to Functional Uterine Bleeding

Definition of Functional Uterine Bleeding

The term "functional uterine bleeding", or "dysfunctional uterine bleeding" as some prefer to call it, is usually applied to cases of abnormal uterine bleeding occurring in the absence of any palpable lesion of the reproductive organs to explain it. On the other hand, Béclère (1934, 1938) and Huffmann (1942) speak of functional uterine hæmorrhage due to genital infection. Brewer and Jones (1948) say that, although most authors include under this designation only those cases in which there is no associated gross pelvic pathology, they believe that it can occur irrespective of the presence or absence of gross pelvic pathology and that the ovarian and endometrial changes are identical in each case. Smith (1944) is of the opinion that the use of the term "functional" is an admission of ignorance concerning the true cause of the bleeding.

Widely differing views have been expressed regarding the desirability of routine diagnostic curettage in cases of presumed functional hæmorrhage, and a number of writers go so far as to advise against this procedure in younger patients. Recently (Sutherland, 1949*a*), I stressed the fact that a diagnosis of functional bleeding should not be made, irrespective of the age of the patient, until curettage has been carried out and the endometrium has been examined histologically. In that paper an analysis is made of the endometrial histology in 1,000 cases of abnormal uterine bleeding occurring in the absence of gross pelvic pathology. All patients with bleeding after the menopause and all types of abortion were excluded but cases in which slight cystic enlargement of one ovary was found and cases showing slight symmetrical uterine enlargement were included in the series.

In 139 instances organic pathological lesions of the endometrium were found, chronic endometritis occurring in 110 cases, uterine polypi in 11 cases, tuberculosis in 10 cases and malignant disease in 8 cases. The endometritis was invariably of the interstitial type and a diagnosis was made only when the endometrial stroma showed infiltration with lymphocytes and plasma cells in appreciable numbers. 8 of the 11 polypi were of the mucous endometrial variety, 2 were fibroids and the remaining specimen was of the adenomyomatous type. In all 10 specimens showing tuberculosis the infection was of the miliary variety, which I described in detail in 1943; one of the patients with tuberculous endometritis was 19 years old. 7 of the 8 patients with malignant disease had carcinoma of the uterine body and the eighth, aged 36, had a round-cell sarcoma.

In the remaining 861 cases the endometrium did not show any histological evidence of organic disease. Endometrial hyperplasia occurred 265 times, irregular ripening of the endometrium 26 times, irregular shedding of the endometrium 13 times and endometrial atrophy 10 times; the remaining 547 specimens appeared normal. No attempt was made in any instance to obtain endometrium at any particular time in the menstrual cycle, the patients being admitted to hospital from the waiting list in the usual way and operation being performed as soon as possible after admission. In view of this, it is worthy of mention that secretory changes were observed in 263 of these 547 endometria.

Although, for the present purpose, these 861 cases can be regarded as functional, it is probable that, in some instances, this is not so. In recent years a good deal of work has been done on the relationship between uterine bleeding and various types of blood dyscrasia, and detailed blood examination was not carried out in any patient in my own series. The possibility of the existence of a pelvic cause of the bleeding which is not apparent on clinical examination must also be kept in mind. As an example of this, Cianfrani (1946) reports a case of uterine bleeding in a patient aged 23, which was found to be due to the presence of a granulosa-cell tumour of the ovary, measuring only 3 mm. in diameter.

Literature on Œstrogen Therapy in Functional Uterine Bleeding

Under the second heading I should like to review briefly the existing literature on the use of œstrogen therapy in functional uterine hæmorrhage. Treatment of this condition with œstrogen preparations is of relatively recent origin. For a number of years it was thought that all, or at any rate most cases of functional bleeding were associated with endometrial hyperplasia and a relative excess of œstrogen, and that it would, in consequence, be illogical to employ œstrogens in its treatment. It is now apparent from my own figures and from many recent publications that the incidence of hyperplasia is much less than was previously supposed and that abnormal bleeding can occur from any type of endometrium.

Although some writers do not regard œstrogen treatment of functional bleeding with favour, it has become increasingly popular in recent years. The leading advocate of this

method is Karnaky, who has written many papers on the subject since 1939 (1939 with Thomas; 1940, 1941, 1943, 1944 *a* and *b*, 1945, 1946). He explains the action of œstrogens in these cases as follows:

> "At a certain estrogenic hormonal blood level which varies in each individual and locality, a constriction of the spiral arteries of the endometrium occurs. This leads to anæmia, dehydration, anoxæmia, necrosis, dilatation of the spiral arteries and subsequently to bleeding or menstruation. A woman bleeds or menstruates only when the estrogenic hormones reach a certain blood level, above and below which the woman is amenorrhœic, regardless of the condition, size, position, shape or contents of the uterus."

Karnaky has used several œstrogens in varying dosages in the course of his work, though fairly large doses are employed throughout. He claims that functional bleeding can be arrested by the use of œstrogens orally, intramuscularly, or injected into the anterior lip of the cervix and supports this claim with some very impressive results in large series of cases. An example of his results is the control of 400 cases in half an hour to twelve hours using 15 to 100 mg. diethylstilbœstrol orally or comparable doses of progynon B intramuscularly (1944*a*). In 1945 he emphasized the safety of diethylstilbœstrol, stating that he had used this drug in the treatment of 3,227 patients with various complaints and had had no serious disturbances. A point worthy of mention is that many of his patients with functional bleeding were also given thyroid and lipoiodine and it is not possible to state what part these substances played in his results.

A number of other writers have advocated œstrogen therapy in functional hæmorrhage although in some instances the figures quoted are too small to be significant. Good results, mostly using oral œstrogens of various types, are reported by Douglas and Imerman (1941), Palmer (1941), Pratt (1941), Cuyler, Hamblen and Davis (1942), Hamblen, Hirst and Cuyler (1943), Rubenstein (1943), Turner, Davis and Hamblen (1943), Hamblen and Davis (1945), Patton (1945), Joël (1946) and Ross and Gill (1948).

Apart from the use of œstrogens in functional bleeding in general, Holmstrom and McLennan (1947) have employed this treatment in irregular shedding of the endometrium. As this condition is characterized by prolongation of bleeding from progestational endometrium, administration of œstrogenic substances during the bleeding phase might be expected to speed up the process of regeneration. The results obtained by these workers in a small number of cases were disappointing but they feel that this form of treatment has not yet been adequately tried out.

Several writers have employed a combination of one of the œstrogens and either progesterone or pregneninolone, the drugs being administered cyclically. Satisfactory results with this treatment in small series of cases are reported by Hamblen (1939), Hamblen, Powell, Cuyler, and Pattee (1940), Hamblen, Cuyler, Pattee and Axelson (1941), McGinn (1942), Bickers (1944 and 1946) and Goldzieher, Haus and Hamblen (1947). The results obtained with this combined therapy have been generally satisfactory and while the hæmostatic effect does not appear to be better than that obtained using œstrogens alone, some workers find that an appreciable number of patients show a return from an anovulatory to an ovulatory cycle.

Comparison with other methods shows that no other form of conservative treatment has produced better results than those claimed for œstrogen therapy. Last year (Sutherland, 1949*b*) I reviewed the literature on functional uterine bleeding since 1938. Most of the papers which appeared during this period deal with the treatment of the condition, and a striking feature is the remarkable variety of therapeutic measures advocated by different writers. Comparison of results is rendered extremely difficult owing to differing conceptions of what is meant by "functional bleeding", inadequate diagnostic criteria in some instances and the small size of many of the series of cases. In view of the fact that a substantial percentage of success is claimed for almost every type of treatment, it is impossible to avoid the conclusion that many of these cases are self-limiting or that recovery is sometimes brought about by psychological means.

Œstrogen Therapy in Functional Uterine Bleeding

Under the third heading I shall indicate briefly my own impression of the place which œstrogens should occupy in the treatment of functional uterine hæmorrhage. As I have already emphasized, all cases of presumed functional bleeding should have a preliminary diagnostic curettage in order to eliminate unsuspected organic conditions of the endometrium. In those patients with a reasonably regular menstrual cycle, the best time to carry out this procedure is the premenstrual phase. I have shown in a previous paper (Sutherland, 1943) that curettage at this time will afford the best chance of detecting tuberculosis. In

addition, irregular ripening of the endometrium will be apparent and anovulatory bleeding from a proliferative phase endometrium can be diagnosed. In cases in which premenstrual curettage reveals no endometrial abnormality, it may be necessary to repeat the operation during a subsequent spell of bleeding on or after the fifth day, in order to find whether the cause is irregular shedding of the endometrium.

Having eliminated organic disease of the endometrium, the remaining cases should be followed up. It will be found that a considerable number have been cured by the curettage, although the exact mechanism by which this is brought about is uncertain. Perhaps the curettage causes an endocrine readjustment leading to normal menstruation in some cases, and presumably the psychological effect of the operation plays a considerable part in others. Stander, Javert and Kuder (1942) found that curettage alone resulted in cure or definite improvement in 71 per cent of 283 cases of functional bleeding.

The patients who are not cured or greatly improved by curettage require further consideration. Those who are at or near the menopause form a large group; in my own series, 339 out of 861 patients were over 40 years of age. With very rare exceptions, I feel that either hysterectomy or radiotherapy is preferable to endocrine treatment in cases of persistent bleeding in this age-group. Indeed, in some severe cases in the late thirties it may occasionally be justifiable to perform hysterectomy.

Patients under 20 years of age are not very numerous; in my series only 33 were in this category. I have found that almost all patients in this age-group can be cured by the use of the anti-menorrhagic factor, details of which I have given in a previous paper (Sutherland, 1942). This preparation is administered orally, it is relatively inexpensive and it causes no ill-effects of any kind. In the very few young patients in whom it is ineffective, I have obtained very satisfactory results by the use of cyclic oral œstrogen therapy. The anti-menorrhagic factor may also be used for older patients, but its efficacy diminishes sharply with age and I have almost abandoned its use in patients over 25.

The remaining cases between 20 and 40 years of age can usually be treated successfully with œstrogens, although attention should be paid to the endometrial histology, and the alternative of androgen treatment should be considered in cases showing marked endometrial hyperplasia. I have obtained very good results with oral œstrogens in this group, but the numbers so far treated are too small to be significant.

The very occasional patients who show no improvement after treatment on the lines indicated should be readmitted to hospital for further investigation. This will include detailed examination of the blood, estimation of prothrombin time, estimation of urinary vitamin C, basal metabolic rate, Wassermann reaction and, in the circumstances previously indicated, repeat curettage. Blaikley (1949) recently has drawn attention to the frequency with which menorrhagia is associated with emotional difficulties. He has found that such menorrhagia is particularly common in young women and can be cured by simple psychotherapy. The possibility of a psychological basis for the bleeding must thus be kept in mind and patients who might fall into this category should be seen by a psychiatrist.

In conclusion, I should like to say that I am at present in the early stages of a long-term investigation of functional uterine bleeding and it is possible that some of my views may be considerably altered in the light of further experience.

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Œstrogen Therapy in Pregnancy

Earlier hopes of this line of treatment have proved unjustified and the premises on which they were based have been rudely shaken. In some respects views as to the action and uses of œstrogen have been completely reversed, and it would be wrong to do more than outline some of the modern trends.

Breast Conditions

There is, I believe, only one indication in connexion with child-bearing for which the value of œstrogen therapy has been established and confirmed and that is the inhibition of lactation. There may be argument about the mechanism whereby œstrogen acts but there is none about its efficacy.

Although very much smaller doses are adequate in some women, the amount necessary to produce consistently satisfactory results is not less than 40 to 45 mg. stilbœstrol, or 1·0 to 1·5 mg. ethinylœstradiol (or equivalent doses of other œstrogens), given in divided doses over not less than four days, and preferably longer. The best results are seen if the dose is high at first and then gradually reduced over the course of seven to eight days. Late filling of the breasts is more likely to occur if treatment is of short duration and is suspended suddenly. Although œstrogens are effective in inhibiting lactation, they are much less useful in suppressing lactation already established, and in either case they do not operate if suckling is maintained.

It is claimed that one or two doses of an œstrogen is helpful when the breasts become engorged. Engorgement in any case undergoes spontaneous cure within twenty-four to forty-eight hours and in the absence of any proof to the contrary I suspect that stilbœstrol often receives the credit for what is a natural cure. The use of œstrogen ointment to promote the development of hypoplastic nipples during pregnancy, and to assist the healing of cracked nipples in the puerperium has a more secure theoretical basis but one cannot say more than that it sometimes appears to help.

Stimulation of the Myometrium

Until the last few years the endocrine control of the tone, sensitivity and contractions of the uterine muscle seemed fairly clear. Progesterone was considered inhibiting—as indeed it is in some animals such as the rabbit, whereas œstrogens were regarded as activating—as they are in all species so far tested. It is probably true to say that the uterus of all mammals

including Man becomes quiescent so far as both muscular and endometrial activity are concerned, if long deprived of œstrogen. It was also previously shown that progesterone is present in greater amount in early pregnancy in the human being, tending to fall off towards term, whereas the amount of œstrogen in circulation gradually rises to reach a climax at the onset of labour. A balance of these two hormones seemed adequately to explain the continuance of pregnancy, and a shift in favour of œstrogen seemed likely to be an important factor in determining the onset of labour and the occurrence of strong contractions during labour. This idea became strengthened when it was demonstrated that during most of the gestation period 90% of the œstrogen in the blood and urine is biologically inactive, being combined with glycuronic acid. A short time before labour, however, the major part of the hormone was said to become activated with a resulting sharp rise in the level of free œstrogen (Cohen, Marrian and Watson, 1935). Out of these and other observations developed, not only a theory to explain the onset of labour, but the use of œstrogens in the induction of labour and on the treatment of inertia.

(*a*) *The induction of labour.*—Although œstrogens cause abortion or absorption of the fœtuses in some animals such as mice and rabbits, it has been recognized for at least fifteen years that they will not disturb a normal pregnancy in woman, no matter how high the dose employed (Robinson, Datnow and Jeffcoate, 1935). Nor will they bring about the onset of premature labour. If any further proof is necessary one has only to turn to the recent work of Smith and Smith in the U.S.A. who have routinely administered stilbœstrol to pregnant women, giving as much as 100 mg. a day in the later weeks of pregnancy, without ill-effect. The real question is whether œstrogen will induce labour at term, and the answer is unknown, for who can say whether the onset of expulsive uterine contractions at that time is not spontaneous. Yet, throughout this country, in hundreds of Obstetric Units, women are regularly given œstrogens in one form or another in the hope or belief that they will induce labour. Moreover, the technique frequently employed, namely to give large doses at frequent intervals for eight to ten hours in the expectation of an immediate response, is without physiological basis. Œstrogen does not have an immediate and dramatic oxytocic effect as does posterior pituitary extract. Nearly twenty years ago (Jeffcoate, 1931) it was demonstrated that œstrone has no effect on the contractions or sensitivity of the isolated muscle strip tested *in vitro*, the earlier experiments in this respect having been fallacious because of impurities present in the preparations tested. Œstrogen only acts on the intact uterus and a continuous supply is necessary to produce its effects. It takes ten to twelve hours for the first change in uterine contractions to become apparent in animals and at least twenty-four hours to reach a good response. Indeed the maximum effect probably requires four to five days' continuous administration. If then œstrogens are to be employed in the hope of inducing labour, or of sensitizing the uterus to such an extent as to enable other substances to induce labour, they must be given for four to five days at least, and preferably seven to eight days, at four-hourly or eight-hourly intervals. If perchance labour begins *soon* after treatment is commenced it should be regarded as coincidental rather than the result of œstrogen therapy.

(*b*) *Uterine inertia.*—Uterine inertia, even of the hypotonic type, has never been shown to be due to, or even associated with, a low level of œstrogen in the blood. Yet, on the arguments already mentioned it seemed reasonable to apply œstrogens to its treatment and I must accept some responsibility for advocating this some twelve years ago (Jeffcoate, 1938). At the time, however, I clearly pointed out the difficulties, the most important of which seemed the time factor. In order to build up a high concentration in the blood stream in the shortest possible time one- or two-hourly injections of the œstradiol ester were advised, it being hoped that an initial effect might become manifest within ten to twelve hours, but it was recognized that it could be no more than an initial effect and not a fully developed œstrogen influence. The results then, as now, remain doubtful, if only because it is impossible to control any method of treating inertia. It is clear, however, that when inertia is the result of some mechanical error such as occipito-posterior position or slight disproportion, œstrogen therapy rarely has any effect on uterine action. Moreover further observation leads me to doubt whether it has any significant effect in hypertonic inertia. Occasionally in hypotonic inertia good uterine contractions arise some hours after giving œstrogens, and Murphy (1947) has confirmed this by tocographic records. The situation does not warrant any stronger statement than that, and I would add that with further experience I see fewer and fewer cases of inertia for which there is not some local cause such as malposition, and I now employ œstrogen therapy comparatively rarely. The time is not yet ripe, however, to deny it any place at all.

If, following œstrogen therapy, an inert uterus becomes more active almost immediately, then, as with the induction of labour, it is doubtful whether the treatment should be regarded as successful and this is true even if œstrogens are given intravenously. As long ago as

1933 Reynolds showed in the rabbit that uterine contractions are not altered until at least ten hours after intravenous administration of œstrogen. In recent years I have tried out the effect of œstradiol given intravenously during normal and prolonged labour, sometimes with the uterus exposed as for Cæsarean section. In no case has there been any obvious immediate change in either vascularity or muscular action—and this despite giving as much as 125 mg. at each injection, and 500 mg. within a very short space of time.

The failure of œstrogens to improve uterine contractibility and sensitivity in a large number of cases, and the equivocal results in the remainder, raises the question as to the validity of the underlying theory. And there is good reason for questioning it. Although œstrogen may induce abortion in some animals it does not act by initiating expulsive uterine contractions, but either by interfering with implantation of the ovum, or by disturbing the placenta of the embedded ovum and causing fœtal death. Expulsion is then a secondary manifestation. Moreover it is now clear that in only a few animals such as the rabbit does progesterone depress myometrial activity. In this respect it is of interest to note that my late teacher Blair-Bell (1933), at a time when nearly everyone else was convinced of the inhibitory action of progesterone, repeatedly pointed out that the evidence was contradictory and that the ornithorhyncus, an animal which he often quoted, has for its size one of the largest and most active corpora lutea, and yet the fœtus is continually and gradually being expelled during the whole of pregnancy. This apparent heresy has proved only too true and it is now generally recognized that the uterus of woman, and of several other animals, is not inhibited by progesterone, nor is its sensitivity to oxytocin reduced. On the contrary, although œstrogen stimulates strong and regular contractions, progesterone produces even stronger if less frequent contractions. Again there is some evidence that the production of progesterone as judged by pregnanediol excretion does not fall significantly at term, and that the levels of œstrogen and progesterone tend to rise and fall together—as might be expected—since their source of production is the same. Moreover only within the last few months, Clayton and Marrian (1950), who originally described the finding of evidence of conversion of conjugated into free œstrogens at the onset of labour, now report that their previous results were erroneous in that the activation of the œstrogens was brought about by contamination of the urine with either blood or liquor amnii. If this contamination is avoided then the urine of women during labour still contains œstrogens which are mostly in a combined and biologically inactive state. Indeed the whole of the evidence on which œstrogens were first employed to induce uterine contractions is becoming suspect, and there is a noticeable tendency in the literature to regard uterine quiescence during pregnancy as being the result of both œstrogen and progesterone—in proper balance. It may be conjectured that if either hormone plays any part in bringing about evacuation of the uterus, progesterone is equally, if not more, important than œstrogen. At least it would seem worth while investigating the effects of large doses of progesterone on the inert uterus in labour. Another tendency, also worthy of comment, is to consider the effect of œstrogen and progesterone on placental function and fœtal nutrition as being possibly more important than any myometrial effect they may have, and for this reason œstrogen alone, or œstrogen and progesterone together, are being used in the treatment of threatened and habitual abortion and good results are claimed (Hamblen, 1941; Vaux and Rakoff, 1945). It is not yet possible to assess these claims but the idea is not without interest. So the wheel turns full circle, starting with a universal idea that œstrogen might induce abortion, and ending with the use of this hormone to prevent abortion.

(*c*) *Missed abortion and missed labour.*—When the fœtus dies, but is retained *in utero*, the situation is rather different because with the cessation of placental function a drop in the level of both œstrogen and progesterone in the blood stream is readily demonstrated. Any hormone then administered might be unhindered in producing its physiological effect on the uterus. The fact that in these circumstances œstrogens administered for five or eight days appear to sensitize the uterus and promote its spontaneous evacuation was discovered almost accidentally (Robinson, Datnow and Jeffcoate, 1935) and much of the theoretical support for it only appeared later. In the reported series (Jeffcoate, 1940) œstrogen therapy was successful in 80% of cases of missed abortion and missed labour. Subsequent experience has confirmed this figure which is now generally accepted by all clinicians who have tried the method. This seems to be one of the most valuable uses of œstrogen therapy, but it should be pointed out that in the original cases treatment was not controlled, nor do I know of any controlled investigation in this respect. It is tempting to enquire whether an equal degree of success would be obtained by giving no treatment at all, or by administering quinine and oxytocin alone, rather than in combination with œstrogen. In view of changing opinions as to the action of œstrogen a controlled investigation should set the matter beyond all doubt; for this work has to be fitted into whatever is the final picture of the hormone control of pregnancy and labour.

Diabetes Mellitus and Toxæmia of Pregnancy

Œstrogen therapy was long ago tried and abandoned for diabetes apart from pregnancy, the idea being to inhibit an overactive pituitary which was thought in some cases to be the cause of the diabetes. One of the most interesting developments in recent years, however, follows the work of Smith, Smith and Hurwitz (1946) and of White (1947) who noted that pregnant diabetics excrete relatively large amounts of gonadotrophin and less œstrogen and progesterone than normal. Œstrogen and progesterone replacement therapy was tried with apparently good effect which seemed in part explained by a reduction in the incidence of toxæmia. This work has not yet been confirmed. In a series of articles Smith and Smith (1948*a*, 1948*b* and 1949) have developed a theory that stilbœstrol brings about increased progesterone production by the placenta because it favours "utilization of chorionic gonadotrophin". They take the view, however, that stilbœstrol acts not by reason of its œstrogenic properties but by virtue of its particular chemical structure, and advise it in graduated doses throughout pregnancy as a prophylactic against the many ills that befall a woman at that time. In their last report they claim to have shown in a controlled experiment that routine treatment of this kind decreased the incidence of abortion, toxæmia, and post-maturity, the number of premature births was not less but premature babies weighed more, and the overall fœtal mortality was lower. Bearing in mind the previous remarks it is interesting to note, however, that the routine administration of stilbœstrol up to term did not influence the behaviour of the uterus in labour—there was no evidence of improved myometrial function. The theory behind all this becomes increasingly abstruse, involving as it does placental function, uterine vascularity and a menstrual toxin theory of toxæmia. It cannot be said to have a secure basis as yet, indeed Davis and Fugo (1947) and Somerville, Marrian and Clayton (1949) have failed to confirm one of the underlying hypotheses, that the administration of stilbœstrol increases the production of progesterone as judged by the excretion of pregnanediol. Nevertheless the work may have something important to offer and large-scale controlled clinical experiments are urgently required to see if the work can be confirmed.

Toxicity of Synthetic Œstrogens

Œstrogens have been put to many empirical uses in pregnancy, such as for excessive vomiting, pruritus, or skin rashes but I would draw attention to another well-established clinical observation which has not yet been explained. Synthetic œstrogens frequently cause nausea, vomiting and other upsets in the non-pregnant woman but never do so during pregnancy or the puerperium, even when administered in daily doses of 100 mg. and more, for many weeks. This raises the difficult problem of the metabolism, detoxication and utilization of these substances, a problem the solution of which might throw light on the function of the œstrogen in circulation during pregnancy, and offer an explanation for some of the apparent contradictions which arise when either physiology or therapy are considered.

In concluding, the position might be summarized by saying that except for the inhibition of lactation and possibly for the induction of abortion when the fœtus is dead, the indications for œstrogens in pregnancy at the present time are experimental, rather than practical.

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Œstrogen Therapy in Primary Dysmenorrhœa

The œstrogens have been employed in the treatment of dysmenorrhœa for a considerable time but some confusion exists regarding the rationale and efficacy of this form of therapy. Some clinicians obtain favourable results by the administration of œstrogen during the first half of the menstrual cycle, whilst others prescribe it during the second half and claim equal success. The œstrogens have also been found effective when administered during the whole cycle. It is difficult to reconcile the almost comparable good results with the varying methods of administration. It is recognized that dysmenorrhœa is not a disease but a symptom-complex and that there is, or may be, a marked psychosomatic element in many cases. If this is true, it can be assumed that treatment, no matter the form in which it is administered, is likely to be efficacious in a proportion of cases, and more especially those in which the menstrual pain is not of marked severity.

We have been studying dysmenorrhœa from many aspects, but recently have directed particular attention to an evaluation of œstrogen therapy. This communication deals with primary dysmenorrhœa which has been considered as synonymous with intrinsic, spasmodic, functional, idiopathic and essential dysmenorrhœa, and is defined as pain at the menses, commencing at the menarche or early years of womanhood, of such a degree as to incapacitate the patient. The selection of cases according to this definition has therefore been strict and only those in which the pain came on a few hours before, at the beginning of, or a few hours after, the onset of the menstrual flow are included. Most of the patients had been treated by various analgesics and antispasmodics and some had even undergone minor surgical procedures before coming under observation.

Material.—There are 38 cases in the series, all of which have been under review for a minimum period of three months and some for a period of over two years.

Table I gives the relevant data concerning the series.

TABLE I.—PRIMARY DYSMENORRHŒA

Total No. of Cases = 38	
Aged 14–28 years	Average 20 years
Menarche 10–16 years	Average 13 years 4 months
Onset of dysmenorrhœa	
At menarche	22 cases = 57·9%
3 months–8 years after menarche	16 cases = 42·1%

Methods of investigation.—A detailed personal and menstrual history and other relevant information was obtained. All patients were instructed regarding the taking and recording of the rectal temperature and were requested to record the temperature daily during the whole time they were under observation. Pre-menstrual endometrial biopsies were performed in all cases where this was possible, and were repeated where necessary during treatment. In the majority of cases no treatment was instituted until the type of menstruation, whether ovulatory or anovulatory, was determined. Thereafter an attempt was made by the daily administration of œstrogen during the first twenty days of the cycle to suppress anterior pituitary activity and thus inhibit ovulation. The initial daily dosage of œstrogen was not always effective in inhibiting ovulation and the dosage had to be increased in subsequent cycles before ovulation was inhibited. Œstrogen was administered during this phase of the cycle not as a therapeutic measure primarily, but in order to confirm the view that inhibition of ovulation is always followed by painless menstruation, and also to form a basis for future therapy. It was felt that if menstruation could be rendered painless, even on one occasion, the patient would be more likely to co-operate in her future treatment and follow-up.

When it was clear from the temperature records or examination of the pre-menstrual biopsy material that ovulation had been suppressed, œstrogen was then administered daily from the fourteenth to the twenty-fourth day of the cycle, and the dosage increased, if necessary, during subsequent cycles according to the effect produced. Generally, post-ovulatory or pre-menstrual œstrogen was not continued longer than a period of three months if no marked alleviation of symptoms was produced. Other methods of treatment were then adopted.

Results.—Table II shows that the menstrual cycle was ovulatory in 33 or 87% of the 38 cases. The temperature record was bi-phasic in 28 patients, and in half of these the endometrium removed pre-menstrually was in the secretory phase. In a further five cases the pre-menstrual endometrium was in the secretory phase. It was impossible to say from the temperature records of the remaining 5 patients whether the cycles were ovulatory or anovulatory.

The records were indeterminate in that the patient proved incapable of recording the temperature accurately or did not co-operate satisfactorily. There was no evidence of hypoplasia of the uterus in any of the cases in which an endometrial biopsy had been carried out.

TABLE II.—PRIMARY DYSMENORRHŒA
METHODS OF DETERMINATION OF OVULATION
Total No. of Cases = 38

Basal temperature record	Pre-menstrual biopsy	No. of cases
Bi-phasic	Secretory endometrium	14
Bi-phasic	—	14
—	Secretory endometrium	5
Indeterminate	—	5

The effect of œstrogen administration daily during the first twenty days of the cycle in 30 patients, who were proved to be ovulating, is seen in Table III.

TABLE III.—PRIMARY DYSMENORRHŒA
EFFECT OF PRE-OVULATORY ŒSTROGEN ON OVULATION AND SUBSEQUENT MENSTRUATION

	Inhibition of ovulation Subsequent period *painless*		Ovulation not inhibited Subsequent period *painful*	
Preparation and daily dosage during first 20 days of cycle	Menstruation at normal time	Menstruation delayed	Menstruation at normal time	Menstruation delayed
Ethinyl œstradiol 0·05–1 mg.	15	2	5*	5
Dienœstrol 1–10 mg.	2	1	0	0

Four patients continued to have painless periods following pre-ovulatory œstrogen. Follow-up shows that two are ovulating and two are not ovulating.

*One had a painless period.

To summarize these results it is seen that the dysmenorrhœa was relieved in all cases in which the dosage was adequate to suppress ovulation, otherwise it was of little value, except in one case. The relief was only temporary as the pain recurred with the next ovulatory cycle, except in 4 cases, or 13% which were apparently cured.

The results of pre-menstrual or post-ovulatory œstrogen therapy are seen in Table IV.

TABLE IV.—PRIMARY DYSMENORRHŒA
RESULTS OF POST-OVULATORY ŒSTROGEN THERAPY

Preparation and daily dosage from 14th to 24th day of cycle		No. of cases	Cured	Relieved	Relapsed	No benefit
Ethinyl œstradiol 0·05–0·15 mg.		22	2	10	6	4
Dienœstrol 3–15 mg.		7	3	1	1	2
	Totals	29	5	11	7	6

To summarize, then, the results of pre-menstrual or post-ovulatory œstrogen therapy: 55% of cases were cured or relieved, but 24% relapsed. 21% of cases received no benefit from this form of therapy.

DISCUSSION

It is significant that there was no evidence of hypoplasia in any of the cases in which it was possible to measure the length of the utero-cervical canal. This is not surprising as it is now recognized that hypoplasia of the uterus, which in the past was considered a common cause of dysmenorrhœa and an indication for œstrogen therapy, is rarely found in women with ovulatory menstrual cycles. It is also of interest and significance that in all the patients in whom ovulation was inhibited the succeeding period was painless. It is unlikely that there was not one or more neurotic patients in the series and yet the suppression of ovulation gave them a period free from pain. This finding does not exclude the psychosomatic factor in dysmenorrhœa, but suggests that the pain is not psychosomatic in origin, but is due primarily to some other cause and that the psychosomatic factor supervenes as a result of the recurring menstrual pain.

Our findings support the contention, which is difficult to refute, that unopposed œstrogen-induced bleeding is painless, and further indicate that primary dysmenorrhœa is always preceded by ovulation. It does not infer, however, that menstruation preceded by ovulation is always painful: this, we know, is far from true. If then the suppression of ovulation promotes painless menstruation, it must be the intervention of the luteal hormone—progesterone—which determines whether menstruation will be painful or free from pain. Now the majority of menstruating women ovulate but do not have dysmenorrhœa. It can only be inferred that menstruation is painless in these cases because œstrogen and progesterone are in equilibrium and synergistic one with the other. Dysmenorrhœa arises when this synergism is disturbed. The imbalance is most probably associated with an over-production of progesterone rather than œstrogen, as an overriding action of œstrogen promotes painless menstruation. Our temperature records tend to support this view, as the basal temperature in several instances did not fall at the onset of menstruation but was maintained during the first day. Confirmation, however, must await the development of more accurate methods for the estimation of small amounts of œstrogen and progesterone in the blood and urine.

Studies in myometrial activity indicate that menstrual pain is due to a hyperactivity or inco-ordinate hypercontractility of the uterine musculature. Now the disordered activity of the uterus, which causes the pain, cannot be due to œstrogen as we have seen œstrogen-induced bleeding is painless, therefore progesterone, or a product of progesterone metabolism, or a chemical substance elaborated in a secretory endometrium, is probably the activating factor in painful uterine contractions. All degrees of menstrual pain, from slight to incapacitating, can thus be explained on the basis of the extent of the œstrogen progesterone imbalance.

Although the uterus is under the control of the autonomic nervous system, there is no general agreement as to the exact innervation of the uterus or segments of the uterus. It may be said, however, that according to present physiological concepts, the activity of an organ under autonomic nervous control is a result of a balance between the parasympathetic and sympathetic nervous systems, or between acetylcholine released by the parasympathetic and the chemical substances—adrenaline-like in effect—released by the sympathetic nervous system. In this connexion it is of interest to note that Reynolds (1939) has shown—although it has not been confirmed in this country—that in the rabbit the administration of œstrogen causes liberation of acetylcholine through inactivation of cholinesterase. The result is hyperæmia and bleeding. It is possible, therefore, that the œstrogens are parasympathetic stimulants and the fact that œstrogen-induced bleeding is painless suggests that the parasympathetic control of the uterus is inhibitory, at least to the cervix. If this assumption is correct, then it follows that progesterone may have the opposite effect and act under certain circumstances as a sympathetic stimulant. Over-stimulation of the sympathetic control of the uterus would not only cause marked vasoconstriction of the vessels, but also hyperactivity of the musculature, especially in the region of the internal os.

These considerations indicate that until we know more about the concentration of the ovarian hormones in painless ovulatory menstrual cycles, œstrogen therapy can only be of limited value in the treatment of dysmenorrhœa. Nevertheless, pre-menstrual œstrogen therapy does help a considerable proportion of cases and should be considered before operative procedures are employed.

I wish to acknowledge my indebtedness to Dr. Maurice Noble and Sister M. Isdale for their co-operation and help in this investigation.

REFERENCE

REYNOLDS, R. S. M. (1939) *J. Physiol.*, **95**, 258.

Section of Physical Medicine

President—H. A. BURT, M.B., B.Chir., M.R.C.P.

[*December* 14, 1949]

DISCUSSION ON THE ROLE OF PHYSIOTHERAPY IN THE PREVENTION AND TREATMENT OF POST-NATAL DISORDERS

Mr. J. H. Peel: I should like to begin by enumerating certain general principles:

(*a*) No amount of physiotherapy after a confinement can replace good obstetric management during pregnancy and labour. One of the commonest of post-natal disorders is prolapse of the uterus and vaginal walls. Bad midwifery may bring in its train a series of consequences that cannot possibly be reversed by any measure of physical treatment at our disposal.

(*b*) Team work is very important. The obstetrician and physiotherapist should agree on a general plan which, however, may need modification to suit individual cases.

(*c*) The results of physiotherapy might be a good deal better if its limitations were more clearly understood by those requesting and those carrying out the treatments. This implies careful selection of cases and, as obstetricians, it is our duty to state definitely that a particular patient has a disability which requires surgical or other treatment rather than physiotherapy.

(*d*) Can the application of physical medicine to the puerperium enable us effectively to shorten the lying-in period? The problem is whether with intensive physiotherapy we can discharge our patients back to their daily routine of work more rapidly.

I would agree that early ambulation is important in preventing thrombosis and valuable in maintaining and restoring the morale of the patient, but I doubt whether it is a sound principle to send patients out of hospital any earlier, even with the maximal aid that physiotherapy can give to the restoration of natural functions. It is impossible to hasten the processes of healing and involution in the genital tract. I would stress the vitally important function of rest and relaxation during the lying-in period. I should like to put in a plea not so much for starting physiotherapy earlier in the puerperium but for carrying it on longer. Because of the fact that the vast majority of patients have to resume their responsible duties within two or three weeks of confinement, I am firmly convinced that properly applied methods of physical medicine are of great value to many post-natal disorders.

Value of physiotherapy in prophylaxis:

(i) Breathing exercises. These must be started within twelve hours of delivery and carried out regularly by the patient. They minimize the risk of pulmonary collapse if the patient has had an anæsthetic and minimize intestinal distension.

(ii) Limb exercises. These exercises combined with early ambulation minimize the incidence of thrombosis if started early and carried out conscientiously.

(iii) Abdominal and postural exercises. These are valuable in the prevention of laxity of the abdominal wall and postural backache. They must be carried out long after the patient leaves hospital.

(iv) Pelvic floor exercises. These are of value in the prevention of prolapse but again must be carried on for some months.

I will now consider certain well-recognized symptoms following childbirth and consider their relationship to physical medicine.

(1) *Low Backache*

In the vast majority of cases this post-natal low backache is due to postural lumbosacral strain. Before making this diagnosis it is necessary to exclude two gynæcological conditions.

(*a*) *Retroversion.*—This condition causes a sense of pressure on the rectum, a sensation of lowness or dragging in the pelvis, sometimes pain in the groin and a sense of pressure at the bottom of the sacrum.

It does not cause lumbosacral backache.

(*b*) *Cervicitis and parametritis.*—This condition may cause discomfort in the iliac fossæ and around the whole pelvic girdle. It is usually accompanied by vaginal discharge and tenderness of the cervix. If, therefore, these two conditions can be excluded in patients complaining of low backache then the patient should be referred to the physiotherapist for remedial postural exercises.

(2) *Stress Incontinence of Urine*

It is now recognized that most of these cases are due to a greater or lesser degree of prolapse of the bladder neck and posterior urethra from their normal anatomical relation to the symphysis pubis. This, in turn, is due to over-stretching or damage to the pelvic vesico-vaginal fascia and pubo-cervical muscles. A slight degree of such injury may follow a first confinement. In addition the normal reflex contraction of the pelvic floor muscles does not take place when the patient coughs. If we examine these patients we can see a bulge of the anterior vaginal wall and the posterior urethra when the patient strains. We have for many years at King's College Hospital employed a combination of pelvic floor exercises and faradic stimulation of the pelvic floor muscles.

We are convinced of the value of this treatment in early cases without any great degree of anatomical prolapse. Cases likely to do well are: (*a*) Those cases with only slight descent of the anterior vaginal wall.

(*b*) Cases with good levator muscles, even though the normal pelvic floor reflex has been temporarily reversed.

(*c*) Cases in which the onset of the symptoms is recent, for example following first confinement.

(3) *Prolapse*

It is important to remember two factors concerned in the ætiology of prolapse.

(i) Damage to the cardinal and other ligamentous supports of the uterus, chiefly associated with uterine descent.

(ii) Damage to the pelvic floor muscles, chiefly responsible for vaginal prolapse. In the post-natal period it is possible to combine physiotherapy with the insertion of a ring pessary inserted to support the uterus itself. The ring pessary lies in the vagina above the levator ani which can contract efficiently in spite of the presence of the ring pessary. On the other hand, it is useless to employ physiotherapy in an attempt to cure a long-standing prolapse in a woman who has had several children.

(4) *Separation of the Recti and Loss of Tone of the Abdominal Muscles*

Exercises and faradism improve the condition of these muscles which in turn is helpful in relieving postural backache.

(5) *The Value of Diathermy and Heat*

There are certain well-defined conditions that occur during the puerperium in which I consider that the addition of these physical agents to our other methods of treatment are a very real advantage to the patient.

(*a*) *The infected and broken-down perineum.*—Usually due to infection or imperfect technique in the primary suture. Heat and diathermy are of great value in hastening the resolution of the infective process and promoting more rapid healing.

(*b*) *Painful perineum.*—The completely healed perineum may remain painful from scar tissue. Short-wave diathermy and radiant heat are of value in relieving the symptoms.

(*c*) *Acute and subacute pelvic cellulitis.*—This condition is often encountered in a mild subacute form causing discharge and pelvic pain. I have found short-wave pelvic diathermy invaluable in treating this sort of case.

(*d*) *Mastitis.*—Short-wave therapy must be given very early if it is to prevent suppuration. It should be combined with the administration of penicillin. In neglected cases with a hard indurated mass diathermy will often hasten localization.

(*e*) *Infected wounds of the abdominal wall* following Cæsarean section. Short-wave diathermy is invaluable in treating this condition.

Finally, from an obstetric point of view I should like to refer to strain or even subluxation of the sacro-iliac joints, the lumbosacral joints and the symphysis pubis. Traumatic strain of these joints during the course of labour is far less common than it used to be because the high forceps is very seldom practised. The processes of softening of the ligamentous supports of the pelvic joints under the influence of the hormone relaxin are progressive throughout pregnancy. This has been shown by X-rays which show progressive widening of the joint spaces as pregnancy advances. However, the more widely employed lithotomy position for forceps delivery is not without the danger of strain to these joints, a point which should be remembered when moving the unconscious patient into position for delivery. However, most cases which show evidence of strain in these joints usually have symptoms clinically during the last few weeks of pregnancy. In this sense it is not a purely post-natal disorder. Treatment consists in rest and a supporting corset rather than in physiotherapy. However, radiant heat does produce symptomatic relief.

Dr. F. S. Cooksey: Physiotherapy may be used to prevent circulatory stasis and postural defects or to restore function in the presence of post-natal disability. In this sense physiotherapy is part of obstetric rehabilitation and to be effective it must be used early and progressively until the restoration of normal function is secured. By contrast physical agents such as diathermy may be used to relieve pain or to assist the resolution of inflammation and in this form physiotherapy is used only for as long as the indication persists.

The Normal Puerperium

In the past it was customary to start massage and exercises around the fifth day and to progress the exercises in preparation for getting up on the tenth, fourteenth or eighteenth day according to the intentions of the obstetrician. The only value of massage in the normal puerperium is to relieve the stiffness of the buttock and trunk muscles after delivery and to assist the circulation in the feet and legs when fatigue makes the patient disinclined to active movement. It is recognized now that venous thrombosis starts silently in the deep veins of the foot and calf soon after delivery and that prophylactic measures must start immediately. On the other hand the stretched and possibly contused pelvic floor requires a period for rest and recovery before remedial exercises are commenced.

Thus massage for the legs and flanks and circulatory exercises for the feet and legs should start on the first day and the massage may be discontinued by the fourth day. From this time the progressive restoration of tone in the pelvic floor and abdominal wall starts and should be continued until the twenty-first day. The expected date of getting up determines the rate of progression in each case. When ambulant, special attention should be paid to correct posture and to the maintenance of tone in the pelvic floor and abdominal wall whilst walking, lifting and engaging in functional activities generally.

Under modern social conditions when little domestic help is available the restoration of physique during the puerperium is essential if postural backache and vaginal prolapse are to be prevented. The physiotherapist should teach the correct use of rest and relaxation as well as remedial exercises.

The Functional Anatomy of the Pelvic Floor

There is synergic contraction of the levator ani when the glutei are so contracted that the buttocks are adducted and the thighs externally rotated. The maximum contraction is obtained only when the thighs are extended to correspond to standing upright and are externally rotated.

In the nulliparous patient at rest, the presence of the levator ani can be felt through the walls of the vagina as a soft roll of muscular tissue extending from the sides of the pelvis across the front of the rectum. On contraction the free posterior and postero-lateral borders

move upwards and forwards towards the symphysis pubis and the belly of the muscle forms a thick muscular shelf extending from the sacrum to the symphysis pubis. Spontaneous contraction of the levator ani occurs when the patient coughs and voluntary contraction when the buttocks are adducted and the thighs externally rotated.

In parous women the spontaneous and voluntary contraction of levator ani is deficient and may be absent. Even with vigorous remedial exercises it is seldom possible to restore the muscle to the efficiency of the nulliparous state. The reflex contraction of the levator ani when the intra-abdominal pressure is raised by coughing, lifting or other muscular action is frequently lost in the puerperium and in some cases it is not regained spontaneously.

Stress Incontinence and Vaginal Prolapse

When a normal individual coughs hard in the standing position, spontaneous adduction of the buttocks can be felt and this is accompanied by simultaneous contraction of the levator ani. If the same test is made at the post-natal clinic on patients who have not had adequate post-natal exercises it will be found in some cases that the buttocks and levator ani contract weakly or not at all and this is especially common in patients with stress incontinence and early vaginal prolapse.

In some cases the levator ani will respond well to faradic stimulation and a good voluntary contraction is obtained when the patient is taught to adduct the buttocks hence the fault appears to be due to impairment of the normal abdomino-perineal reflex. In other cases little if any contraction of the levator ani can be obtained on faradic stimulation or voluntary effort, but improvement follows after a lapse of some weeks or months suggesting some temporary denervation of the muscle possibly due to ischæmia produced by the pressure of the fœtal head in a prolonged second stage.

It is doubtful if sufficient attention is paid at post-natal examinations to the diagnosis of dysfunction of the levator ani and to prescribing remedial treatment in the early stages. Transient stress incontinence is fairly common and should be regarded as a warning symptom that the rehabilitation of the pelvic floor is incomplete. Persistent stress incontinence may be due to marked prolapse or to ischæmic damage to the internal urinary sphincter. In the former, faradic stimulation and exercises usually fail and the wearing of a suitable pessary, or an operation, may be necessary. In the latter, operative repair is often required but, in some cases, a course of faradism and exercises will succeed and should be given a trial.

In the application of faradism two technical points are important. The motor point of the levator ani is situated about one and half inches within the vagina and is very critical. Correct placement of the electrode can be recognized by feeling the electrode carried forward and upward towards the symphysis pubis with each surge of the current. The indifferent electrode on the hypogastrium should be small and as low as possible on the abdomen to avoid excessive stimulation of the abdominal muscles. Symptoms of minor degrees of vaginal prolapse and stress incontinence are relieved in most cases but descent of the vaginal walls on straining is not materially altered because treatment improves the tone and function of the pelvic floor but does not reduce overstretched tissue.

Lumbosacral Strain

Of the many forms of backache one clearly defined type presents in the post-natal period. The pain is in the lumbosacral region and appears four to six weeks after delivery corresponding to the time when extra domestic help is no longer available and the baby is becoming heavy. The backache increases during the day, especially when overtired, and is relieved by rest. On examination there is tenderness over the lumbosacral joint and an increase in the forward pelvic tilt. The explanation seems to be that fatigue leads to loss of tone in the glutei and abdominal muscles with consequent lordosis and a postural strain of the posterior lumbosacral ligaments.

Exercises to correct the pelvic tilt and a midday rest relieve most cases rapidly if the patient understands the need to correct her posture and avoid fatigue, but in long-standing cases it may be necessary to wear a lumbosacral corset for six months or so.

Undue Laxity of the Abdominal Wall

Surging faradism and abdominal exercises are useful in the treatment of abnormal divergence of the rectus abdominis and undue laxity of the abdominal wall. Large electrodes should be used for the application of the faradic current so as to stimulate the many motor points of the abdominal muscles. A firm and well-fitting corset should be worn to support the muscles until improvement is obtained. Treatment must be intensive and prolonged to be effective in severe cases.

Sacro-iliac Strain

A painful sacro-iliac joint due to softening of the ligaments of the joint during pregnancy is difficult to treat. Diathermy gives temporary relief but the only agent which is really effective is a well-fitting sacro-iliac belt which must be worn for at least twelve months. Manipulation and remedial exercises to mobilize the joint are contra-indicated in the acute stage but may be useful in long-standing cases. It is important to recognize the lesion early in the puerperium and to supply a sacro-iliac belt without delay.

REFERENCE

BELL, J. G. Y., and COOKSEY, F. S. (1937) Faradism and pelvic floor exercises in the treatment of urinary incontinence. *Congr. J. Chart. Soc. Physiotherapy*, p. 27.

Dr. P. Bauwens asked Dr. Cooksey why it was that he specified that the indifferent electrode during his treatment with faradism to the pelvic floor should be applied to the abdominal wall. It struck him as being more logical to put the indifferent electrode on the gluteal muscles, as these were known to be concerned with pelvic floor activity as far as associated movements were involved.

Mr. V. B. Green-Armytage expressed surprise that neither of the openers had made any reference to a condition that was very common—namely ballooning of the vagina after labour. This state, first described by Stacey Wilson, and later by De Lee, was nothing whatever to do with prolapse, nor related to rupture or tearing of the perineum. It was related to a prolonged second stage of labour, that state for which De Lee had stressed the importance of prophylactic forceps. Ballooning of the vagina was (1) often an indirect cause of divorce, for coitus became uninteresting and orgasm was an impossibility; (2) it gave rise to that expression of patients: "I feel as if my inside were coming outside"; (3) it was the source of that most distressing symptom which often a patient will tell a woman, but not a male doctor, namely "that she can pass wind from the vagina" or that "after taking a bath she can expel water"; (4) it is, I believe, one of the causes of recurrent pyelitis.

All these consequences, not mentioned in any of our textbooks, could readily be cured by properly conducted pelvic exercises and intravaginal faradism.

Miss M. Randell: The title of the discussion in my view should be more comprehensive, it should consider the role of physiotherapy in midwifery, thus including pre-natal, natal and post-natal preparation. Modern physiotherapy in midwifery aims at prevention (through self-knowledge) rather than cure. As Dr. Kathleen Vaughan wrote in her book "Safe Childbirth": "The time for exercise is *before* confinement".

The woman of to-day wants to know all about having a baby from her point of view—what is to happen to her—what she has to do about it—will it have harmful effects on her figure, and on her health? It is for this part of her ante-natal preparation that a Chartered Physiotherapist experienced in this branch of medicine could be delegated to teach simple applied anatomy, physiology, psychology, and the theory and practice of relaxation, movements, and postures. With this knowledge and a sense of responsibility thus gained, the expectant mother will come into labour, fearless, self-disciplined, and emotionally self-controlled, to co-operate with obstetrician or midwife in making her labour easy, safe and natural.

Dr. P. Dingle emphasized the incorrect stance or position adopted by large numbers of pregnant women after the 28th week of pregnancy—frequently there is a marked lumbar lordosis. This lordosis may be increased by ill-fitting "maternity corsets" bought off the rack, and put on in such a way as to press the enlarging abdomen downwards and forwards. Advice and supervision of the fitting of this corset by assistants at a clinic would be an advantage. After the lying-in period the mother should not only receive strengthening exercises but her carriage, when she begins to get about, should be watched. Having walked with a lordosis for so many months her spine needs to be readjusted, or with each pregnancy there is an increasing displacement which may be the basis of gynæcological backache in later life.

Dr. Cooksey, in reply, agreed with Dr. Bauwens that in the treatment of the pelvic floor by faradism the indifferent electrode could be placed on the glutei. He used the abdomen because the latter often lacked tone. Probably the best arrangement would be to divide the indifferent electrode between the abdomen and glutei.

[*April* 12, 1950]

SYMPOSIUM: THE TREATMENT OF FACIAL PARALYSIS

Miss Josephine Collier, F.R.C.S.:

The object of this paper which is based on an analysis of the records and photographs of 46 patients with facial paralysis is to examine the defects of present methods of treatment and to find how the standard of recovery can be improved.

The first consideration in the treatment of facial paralysis must be the nature of the nerve lesion—degenerative or non-degenerative, or a mixed lesion with degeneration involving only some nerve fibres. Immediate assessment of denervation is not possible; we must wait for the qualitative and quantitative changes described by Erb, or for the onset of fibrillation as shown by electromyography, that is, ten to fourteen days may elapse before we can know that degeneration is inevitable. An earlier diagnosis of the onset of degeneration in some fibres may be more important in the facial nerve than in nerves of the limbs because of its peculiar situation in a rigid bony canal. It has been shown that the damaging effect of pressure on nerve is due to occlusion of the blood vessels (Denny-Brown and Brenner, 1944). Ischæmia interferes primarily with the myelin sheath and has at first little influence on the Schwann cells and axis cylinders. At this stage the changes are reversible—the so-called physiological block which can be followed by perfect recovery of function. If, however, pressure is continued vascular stasis occurs in neighbouring segments of the nerve causing œdema above and below the site of compression. This œdema and increasing obstruction in the blood vessels lead not only to interference with the progress of repair in the compressed segment but to complete degeneration involving axis cylinders and Schwann cells.

We need more exact tests in the early stages of paralysis if we are to discover whether these theoretical considerations are of clinical importance, i.e. do ischæmic lesions, however produced, commonly develop into degenerative ones? And if so would relief of pressure during the early stages of ischæmic block prevent the occurrence of degeneration?

Bell's Palsy

More than one pathological process may produce spontaneous facial paralysis. Since cases tend to appear in groups or small epidemics and are sometimes associated with herpetic eruptions, not only of geniculate ganglion origin but with zoster involvement of other ganglia, it may be asked whether most cases are of virus origin. The occurrence in children of cases indistinguishable from Bell's palsy during epidemics of anterior poliomyelitis has been observed. The possibility of a nuclear origin of facial paralysis should be borne in mind by those inclined to recommend decompression of the nerve.

Hæmorrhage in the fallopian canal in patients with hypertension, similar to conjunctival and retinal hæmorrhages, may be responsible for some cases of sudden peripheral facial paralysis. There is post-mortem and clinical evidence for this group (Merworth, 1942). Few cases of Bell's palsy come to autopsy. Those reported suggest that there may be a neuritis and a poliomyelitis (Denny-Brown *et al.*, 1944). This would explain the alterations in the cerebrospinal fluid that are sometimes found.

We cannot get any clear evidence of the morbid anatomy from the findings reported on decompression of the nerve. It has been variously stated that the nerve is swollen even up to two years after onset (Morris, 1938) or that there is a constriction at the stylomastoid foramen with swelling of the nerve immediately above it or if the paralysis had been present for more than six months that the nerve in the neighbourhood of the stylomastoid foramen is shrunken (Cawthorne, 1946).

Kettel (1947), after operating on over 50 cases, believes that a lesion of the vasa nervorum is responsible—a primary ischæmia that leads to secondary œdema of the nerve and necrosis of the neighbouring bone if the ischæmia is prolonged.

I have never found swelling of the nerve; perhaps that is because I have never operated earlier than three months after onset. I have sometimes observed a normal nerve, sometimes fibrosis at the stylomastoid foramen or scar extending over the whole vertical course. Regeneration has occurred after decompression of an apparently normal nerve or after incision of scar tissue; in other cases with similar findings there has been little or no return of movement.

Diagnosis of the exact site of the lesion and of the state of the nerve should precede operation. If the lesion is accessible, i.e. in the fallopian canal, will decompression help?

Some would operate on every patient with a negative faradic response or if there is no sign of recovery within some arbitrary period such as six weeks. I think there are a number of fallacies here. If we are to take a negative faradic response as indicative of total degeneration then recovery must be by regeneration which is bound to take time and will in any case be associated with the defects of reinnervation, i.e. there will be synkinesia and wasting, and decompression will not eliminate these. *The belief that decompression performed say eight to ten weeks after onset of paralysis has been responsible for recovery of movement in a few days does not take account of the rate at which regeneration occurs.* Such cases are probably ones of reversible ischæmic block or of mixed character. Accurate electrical testing and electromyography should elucidate these. It is probable that ischæmic block can persist for several weeks. If fibrillation action potentials are absent or few in number or if motor units are obtained on insertion of the needle, operation on the nerve is not justified. Since I have had the assistance of electromyography I have not seen any case of Bell's palsy that called for decompression.

Decompression or the insertion of a nerve graft cannot eliminate misdirection or branching of regenerated axons and thus prevent or abolish synkinesia. There are occasional cases that remain permanently paralysed. I am inclined to think that these patients with persisting paralysis should be treated by a combination of facial-hypoglossal anastomosis and plastic surgery. All cases as I shall show later should have physiotherapy from the onset.

Facial Paralysis Secondary to Trauma and Disease

When facial paralysis follows injury or disease in the temporal bone or in its course outside the stylomastoid foramen we must first diagnose the nature of the nerve lesion and if degenerative the possibility of spontaneous recovery. For prognosis in degenerative cases we cannot always obtain an immediate answer from physical medicine but there is often indirect evidence to indicate the need for early exploration. The nature of the causative disease may itself be an indication for operation—for example the occurrence of facial paralysis in the course of chronic suppurative otitis media calls for a radical mastoid operation. Here there is no need to expose the nerve unless the presence of œdematous granulations and cholesteatoma has obliterated the normal landmarks. In such a case uncovering the nerve, beginning from below well away from the affected part, will relieve the pressure on the nerve in safety. *The sheath of the nerve should not be opened;* to do so may lead to intraneural fibrosis from spread of infection to the nerve tissue. I have known this happen in several cases and have found subsequently a segment of nerve so fibrosed that there was no possibility of axons entering the peripheral end and resection and grafting have been necessary. When facial paralysis follows injury such as a fractured skull, a gunshot wound or a mastoid or parotid operation we can often form an opinion on the improbability or impossibility of spontaneous regeneration by considering the history and nature of the injury (and in operative trauma the surgeon's report is of paramount importance). I need not pursue this aspect of the problem which may be purely an otological one but the time and mode of onset of the paralysis are important. Complete facial paralysis following immediately on trauma implies severe injury to the nerve, either division or compression which will be followed by degeneration, the cause of which may persist and prevent regeneration. Evidence of the time of onset is, however, of value only if the presence or absence of paralysis has been looked for and noted in the records. Facial paralysis is sometimes missed in an unconscious patient with a bandaged head. This applies to patients with head injuries as well as after mastoid operations. I have on several occasions operated on patients whose facial paralysis was said to have first appeared the day after operation or even thirty-six hours later and have found complete separation of the ends of the nerve.

As far as these traumatic and otological groups are concerned regeneration can be brought about by direct operation on the nerve, either nerve grafting if there is actual section and separation of the cut ends or impassable scar, or by that type of neurolysis which in the temporal bone is called decompression, implying uncovering the nerve in its bony canal, with removal of adherent scar or fractured bony fragments. The possibility of successful reinnervation of the facial muscles by these means is now well established provided the central and peripheral ends are accessible. Regeneration is facilitated as in any nerve operation by an operative technique that minimizes formation of scar tissue (Collier, 1949).

Defects of Reinnervation

But successful regeneration of a motor nerve does not necessarily mean satisfactory recovery of movement. This applies particularly in the face where symmetry with the opposite side is so important. Regeneration is inevitably slow, and wasting and stretching of the muscles during denervation are responsible for persisting weakness. In addition diffuse



FIG. 1.



FIG. 2.



FIG. 3.

(Mrs. W.)—FIG. 1. Complete degenerative lesion of left facial nerve from cholesteatoma and mastoid trauma. FIG. 2. Good recovery of voluntary and emotional movements in lower face after decompression and regular physiotherapy. FIG. 3. Wasting of levator labii superioris alæque nasi, frontalis and corrugator supercilii.



FIG. 4.



FIG. 5.



FIG. 6.

(Miss P. N.)—FIG. 4. Complete degenerative lesion of right facial nerve from mastoid trauma (8 mm. gap in nerve). FIGS. 5 and 6. Four years after insertion of 12 mm. graft. Irregular physiotherapy. Good reinnervation but limited movement all muscles of lower face due to wasting.

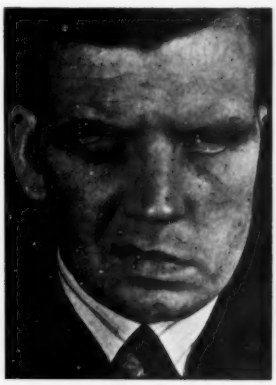


FIG. 7.



FIG. 8.

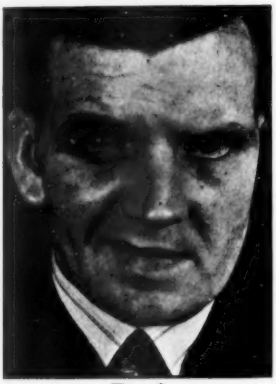


FIG. 9.

(Mr. W. G.)—Left facial paralysis after aural opn. 1935. Radical mastoid opn. 1937. Patient was told facial nerve was intact and would recover. No physiotherapy. Electromyography 1948. Loud motor units in orbicularis oculi and muscles of lower face. No fibrillation, i.e. reinnervation but owing to wasting and stretching during denervation the nerve impulse cannot produce useful contractions. FIG. 7. 1948. At rest appearance of complete facial paralysis. FIG. 8. Slight voluntary movements with effort. FIG. 9. Slight movement on smiling.

distribution and misdirection or branching of regenerated axons produces that peripheral confusion we call synkinesia or mass movement. This occurs in varying degrees whether movement returns spontaneously or as a result of operation. The quality of the recovery after degeneration may also be marred by muscle spasms and by contractures.

Since symmetry with the opposite side of the face requires a standard of recovery necessarily high we must consider the special character of the facial musculature and how far treatment can be expected to prevent or limit these disfigurements.

In the first place the facial muscles are particularly thin and delicate, they lie directly under the flexible and elastic skin and are inserted either into the skin or attached to the lips and eyelids. The beautiful coloured illustrations of our textbooks are misleading as they necessarily represent an idealized picture after removal of the skin. Unlike the skeletal muscles the facial muscles are not compact structures bound together by a clearly defined muscle fascia but lie in the subcutaneous tissue with the muscle bundles thinned out with no veil-like covering of superficial fascia as is found in other parts of the body. Ernst Huber of Johns Hopkins (1930) first drew attention to the importance of the absence of muscle fascia in enabling small parts to contract independently of the rest of the muscles and in varying combinations with parts of other muscle groups, thus permitting a multiplicity of shades of facial expression. Is it surprising that restoration of movement after total denervation with all the hazards of regeneration is far from perfect?

Facial expression involves complex reflex mechanisms, controlled or modified by the highest cortical centres. Sir Charles Bell wrote about the Philosophy of Expression or "the changes in the human countenance which accompany the exercise of the mind". Emotional stimuli produce spontaneous contractions of these voluntary muscles but spontaneous expression of emotion is variously controlled by age, education, race and temperament. An important consideration for our discussion is the possibility of acquiring control of spontaneous emotional movements.

The changes that occur in the limb muscles on denervation have been investigated in animals by Gutmann and Young (1944) and by means of muscle biopsy in man by Bowden and Gutmann (1945). Nothing comparable has been done for the face but denervation is likely to give the same histological picture if not an exaggerated one because of the delicate character of the facial muscles. Shrinkage of the muscle fibres is associated with progressive increase of connective tissue, until ultimately all the muscle is replaced by connective tissue and fat and the changes then are irreversible. The rapidity with which wasting occurs in the facial muscles on denervation is obvious. There is frequently no galvanic response and no fibrillation in the frontalis when muscles in the other parts of the face are still contractile and this is associated with the failure of recovery of function in this muscle even when satisfactory regeneration of nerve occurs and adequate reinnervation of the lower part of the face follows. Levator labii superioris alæque nasi often fails to recover because atrophy has become permanent. Figs. 1, 2 and 3 show that despite a fairly satisfactory return of emotional and voluntary movement to the lower face as a whole, voluntary efforts to wrinkle the nose are unsuccessful. This contributes to the general asymmetry of expression.

Other muscles whose permanent paralysis or weakness may mar the quality of the result even with good regeneration of nerve are those inserted into the upper and lower lips—this is very apparent in laughing where the complete relaxation of orbicularis oris gives an uncontrolled power to the other muscles which concentrate on the mouth (Figs. 4, 5 and 6). Again with good nerve regeneration there may be sagging of the lower eyelid causing epiphora and exposure of the sclera (Figs. 7, 8 and 9).

It is of course possible and indeed probable in some cases that owing to the hazards of regeneration (either of surgical origin or inevitable) that the number of regenerating nerve fibres reaching the muscles are insufficient or of poor quality so that many muscle fibres are never reinnervated. I am not to-day concerned with the surgical aspect of this problem but want to stress the muscle element and to point out that without suitable treatment progressive atrophic changes may not only become irreversible but may actually increase the difficulties of reinnervation as the empty Schwann tubes become embedded in connective tissue and incapable of receiving new axons or of becoming myelinated.

Muscle atrophy from disuse is increased by chronic overstretching which in the case of the facial muscles is brought about by the pull of the muscles of the sound side and by gravity. There is another factor to be considered here: the skin into which the muscles are inserted. This stretching of the skin is particularly important in the elderly patient where the elasticity of the skin is already impaired.

Contractures show in the nasolabial fold and as a dimple in the chin, that is, in situations where the muscles are inserted into the skin though not in the corrugator supercilii region.

There is no evidence that they are brought about by electrical treatment. Actual contraction of newly formed fibrous tissue probably plays no part in facial contracture; when fibrosis is maximal with permanent paralysis there is no contracture. Nor are the muscles permanently shortened; when the patient is relaxed the contracture disappears. Contractures and spasms of the face are probably due to the same phenomenon as synkinesia—branching or misdirection of axons. Disfiguring mass movements and deep contractures are more pronounced in patients with animated mobile faces. The only way to minimize their presence is to encourage the patient to cultivate an impassive face; to achieve this the patient is apt to become more self-conscious which may defeat the object of treatment.

The Role of Physiotherapy

The problem, therefore, in every case of denervated facial muscles—no matter how that denervation has been produced—is to prevent or diminish wasting and overstretching while the nerve is regenerating. There is conflicting evidence about the value of galvanism for the limb muscles but the experience of Gutmann and Guttmann (1942) with the rabbit and of Jackson and Seddon (1945) with the small muscles of the hand in man are I think applicable to the face. The important point that emerges from these investigations is that atrophy of muscle fibres particularly in small muscles can be minimized provided a good contraction is elicited and that the treatment is given regularly and sufficiently soon after denervation. The only value of galvanism is to maintain contractility of the muscle by producing contractions. In this way interstitial fibrosis though not prevented is minimized. This is even more important in the face than in the limb muscles as the action of the thin muscle fibres is easily overcome by increased formation of connective tissue.

Unlike the surgeon dealing with nerve lesions in the limbs we are not concerned with sensory loss, joint stiffness or associated vascular lesions. We have, however, the special problem of stretching of the skin because of the insertion of the facial muscles into the skin itself and the pull from the opposite side. Stretching of the skin can be controlled to a certain extent by methods used to prevent overstretching of the muscles. The conventional hook in the angle of the mouth attached to the ear defeats its object when the sound side contracts by over-stretching not only the orbicularis oris but the elevators and depressors inserted into it. The intra-oral splint originally advocated by Allen and Northfield (1944) and variously modified is a more rational support, which also preserves the nasolabial fold thus limiting stretching of the skin at this site. But this splint does not prevent the drooping of the lower lid nor the stretching of the nasal part of levator labii superioris and the muscles of the lower lip which are responsible for much expressional disfigurement even with good reinnervation. I commit these defects to your particular attention. Support by strapping is seldom effective, it interferes with galvanic stimulation and is ill tolerated during the months of denervation. A partial tarsorrhaphy, useful as an adjunct for masking permanent disfigurement in the late stages, does not prevent stretching of the lower fibres of orbicularis oculi during denervation. Plastic surgery by means of temporary slings of fascia or tantalum wire—if these could be inserted superficial to the muscles without interfering with reinnervation or producing scarring in the skin—would be more effective than any external mechanical support. I do not think we collaborate sufficiently on this problem. Prevention of wasting and stretching should be the concern of the specialist in physical medicine, the otologist and the plastic surgeon and we should not limit the latter to the palliative surgery of complete fibrous atrophy. Occasionally, too, a fascial sling in addition to masking the disfigurement of long-standing paralysis will allow partially recovered muscles to work at better advantage so that previously ineffective movement may become apparent.

Since atrophy is most rapid in the early stage of denervation treatment to limit wasting and stretching should be begun as soon as there is evidence of degeneration of the nerve. The need for an intra-oral splint is as urgent as an emergency operation. The patient should not wait for this as he has to wait for the supply of dentures. There are of course contra-indications to the use of early galvanism, e.g. where pain in the face is a prominent feature in herpetic facial paralysis.

When insisting on the importance of early care of the muscles we should not forget facial paralysis due to head injuries, particularly when the paralysis is immediate and complete. Regeneration occurs in the majority of these but in many cases owing to the long period of denervation there is much wasting and stretching which never recovers.

I do not need to say much about re-education except that the patient should be encouraged from the onset to restrict the movements of the normal side. Cooksey (1941) stressed the importance of avoiding exercises until reinnervation has occurred and voluntary movement is obvious. Unfortunately patients still come from all parts of the country who have been trying vigorously to move a completely paralysed face, grimacing with the sound side and

increasing the stretching of skin and paralysed muscles. When the muscles have an adequate nerve supply, exercises in front of a mirror with the sound side controlled will improve their action. Exercise, however, cannot be a re-education of emotional movements and there is no evidence that this form of treatment can bring about a dissociation of action of muscles which from the mix-up of regenerated axons now work together.

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Dr. John D. Spillane:

All clinicians must have seen examples of Bell's palsy in which exposure to a draught of air clearly provoked the onset of the malady. I recall the case of an airman who fell asleep on a pile of kit in a plane during a wartime flight and was wakened by acute discomfort on the left side of his face and found a ventilator shaft not one foot above him, directing a stream of cold air at high pressure on to his face. He developed a Bell's palsy a few hours later. In such instances no one can deny that chilling of the facial nerve occurs. But in the majority of cases the history is either not definite enough about the possibility of some form of exposure or else it can be ruled out altogether. Were cold *per se* the deciding factor one would expect a greater incidence—both total and seasonal. Seasonal figures, however, show no great variation. I saw more cases of Bell's palsy during the hot summer of 1949 than during the recent—admittedly mild—winter months. Personal experience, of course, is often misleading, but we have all seen small epidemics of Bell's palsy. One new case is followed in a few days or a week by several others. In a small community it should not be difficult to keep a record of the incidence of the disease and of all those factors which, in epidemiological studies, have rewarded the researcher. What Pickles did in the field of infective hepatitis is urgently needed in the case of Bell's palsy. In a country district a physician holding one of the new regional posts would be in an excellent position to make such a study.

Instances of bilateral, recurrent, hereditary or familial peripheral facial paralysis seem to support the idea of a predisposing factor. This may be anatomical—such as a narrow facial canal—but there is little direct evidence of this. The spinal accessory is a purely motor nerve, of course, and it enters the neck through an aperture, but the latter is wider and less exposed and instances of idiopathic palsy of the spinal accessory nerve are rare (Spillane, 1949). Bergström (1946) succeeded in curing a young woman of 35 who had had a Bell's palsy for fifteen years by decompressing the facial canal, which he found was constricted at one point. But there is another possibility. Most neurologists have seen examples of recurrent polyneuritis, with or without facial palsy. I have a patient who four times during the past thirty years has been bedridden with multiple symmetrical peripheral neuritis. He has made a complete recovery on each occasion and in two of them both facial nerves were completely paralysed. The facial nerve is especially liable to be affected in acute febrile polyneuritis, the cause of which is not known. It may be infective or toxic in character. It is unlikely that the factor predisposing to facial involvement in such cases is an anatomical one. In other forms of polyneuritis—such as diphtheritic or in beriberi—the facial nerve nearly always escapes. It seems, therefore, that involvement of the facial nerve depends not so much on its structure or position as on the special qualities of the attacking agent. There seems to be some tropic influence at work. Might not this be a virus?

When Ramsay Hunt (1906) correlated his experience and that of others on the association of herpes of the auricle and facial paralysis, he brought attention to bear on the question whether Bell's palsy itself might result from infection by the virus of herpes zoster. He concluded that the syndrome which has since borne his name resulted from the invasion of the geniculate ganglion by the herpetic virus. In his original cases the herpetic eruption appeared about the meatus but later other cases were recorded in which the rash developed

behind the ear, in the nose or on the palate, fauces or on one side of the tongue. He asserted that these areas must derive some sensory innervation via the geniculate ganglion. Only one case came to post-mortem and the geniculate ganglion was not examined. That the Ramsey Hunt syndrome is due to herpetic geniculate ganglionitis has thus never been proved. Facial palsy in association with trigeminal, occipital or cervical herpes with or without auditory symptoms has been reported on many occasions. They clearly indicate multiple neuritic lesions. Some years ago (Spillane, 1941) I reported a small outbreak of herpes zoster in which there was one case of combined facial paralysis and ipsilateral trigeminal herpes. During the epidemic, while 5 of the cases were in hospital, there occurred the only instance of Bell's palsy seen at the hospital for a period of nine months. He came from the same military unit as one of the zoster cases. Denny-Brown *et al.* (1944) have described a case of auricular and occipital herpes with palsy of the facial nerve which came to autopsy. They found a neuritis of the facial nerve *without any damage to the geniculate ganglion* and typical herpetic changes in the second cervical ganglion.

From these and other studies we can infer that some of the various herpes zoster syndromes with paralysis of the facial nerve result from the concurrent involvement of two or more cranial nerves. The demonstration that the herpes virus can cause a peripheral mononeuritis —with or without involvement of the *corresponding* ganglion—certainly strengthens the view that Bell's palsy may result from virus infection. Serological evidence is meagre. Aitken and Brain (1933) found by complement-fixation tests that in the sera of 22 cases of Bell's palsy zoster antibodies were present only in 4.

Post-mortem observations on cases of Bell's palsy are very rarely recorded. Kettel (1947) was only able to collect four such references. In each case there was no sign of compression of the facial nerve in its canal or of inflammatory disturbance. There was striking degenerative change in the nerve itself—more marked peripherally. In considering the indications for the surgical treatment of Bell's palsy these facts must be borne in mind. Decompression of the canal is said to disclose visible swelling of the facial nerve in some 50% of cases (Kettel, 1947), and how often have we read that on incising the nerve sheath the contents bulged forth as if under pressure. But anyone who has seen nerves exposed, as in the late war, will realize that the macroscopic identification of swelling and bulging of nerve bundles is no easy matter. Personal interpretations differ widely.

Whatever the cause of the lesion in Bell's palsy, we know that in the great majority of cases, variously estimated at between 75% and 90%, it is completely reversible. But statistical estimates are of limited aid when we are confronted with a fresh case. Individual prognosis is difficult. The slighter the paralysis, of course, the better the outlook. And in the younger age-group the prognosis is brighter. It should not be forgotten, however, that in the young person symmetry of the face at rest does not mean that paralysis is not complete. As Bell himself wrote—"the features are duly balanced; but the slightest smile is immediately attended with distortion". In the older patient the experiences of life have left their mark upon the features. The furrows that appear are to a great extent determined by the dominant daily emotions and the resulting muscular tensions. When the skin ultimately loses its elasticity the lines are deep and fixed. But with facial paralysis they vanish and the side of the face sags in unsightly fashion.

While the paralysis is complete ipsilateral contractures do not develop. They usually make their appearance several months after the onset when recovery is beginning. They bring with them certain changes in the features of the patient. In the zygomatic muscles contracture may be marked. The elderly patient may welcome this development for it refashions the lost nasolabial fold and restores some symmetry to the face. But in the smooth face of the young person it brings to the appearance at rest the distortion that formerly appeared only with movement. These disfigurements, which can readily deceive the observer, are usually accompanied by spasmodic facial twitchings and associated movements of overaction. Smiling is attended by closure of the eye on the affected side. The zygomatics may pull out the corner of the mouth when the patient shuts his eyes. Tic-like clonic movements often can be reproduced at will by the patient.

These secondary disturbances are not simply due to electrical treatment as is so often reported. Prolonged faradism or galvanism may make matters worse, it is true, but their development may be seen in the absence of any form of treatment whatever. Starting some five or six months after the onset, these abnormal muscular movements and contractures may develop for a year or more and then slowly subside or become stationary. Contracture is often more permanent than clonic spasm or associated overaction. For many years the question of their origin being centrally or peripherally determined has been debated. Their frequent concurrence suggests that they result from one type of disturbance. Gowers (1888) questioned whether by constant stimulation of the facial nerve nucleus by attempts to move

the face, changes might develop in the nucleus. Ballance (1934) claimed to have observed such changes not only in the facial nucleus but also in the pyramidal cells in the opposite rolandic facial motor cortex of monkeys in whom one facial nerve had been cut. But his former colleague Duel, and Fowler and Wolffe, disagreed (Fowler, 1939). They examined his sections and concluded that the changes in the Nissl substance were artefacts. Earlier, Spiller (1919) had suggested that misdirection of regenerating axons accounted for these muscular phenomena. Horsley thought they bore no resemblance to movements of the face brought about by electrical stimulation of the facial motor cortex. Finally, Howe *et al.* (1937) showed that, experimentally at any rate, the abnormal movements accompanying regeneration of severed facial nerve fibres in the monkey were due to actual branching of axons at the site of injury. This brought about a functional association of facial muscles which were widely separated and which did not normally act in unison.

The development of the facial muscles has reached marvellous perfection in the white man. There is good evidence that the mimetic facial musculature, in contrast to that of the forehead, temples and occiput, is still evolving (Huber, 1931). Power of facial expression may be greatly developed within the lifetime of an individual. A youth who finds he cannot frown without at the same time closing his eyes may, with practice, learn to contract his superciliary and glabellar muscles independently of others. The acquisition and gradual perfection of language must have had a decisive influence upon the evolution of what makes up, to use Bell's own words, "the Anatomy and Philosophy of Expression". Intimately attached to the skin and subcutaneous tissues, possessing no distinct fascia, these gracile slips of muscle are beautifully adapted to their needs. When deprived of nerve supply the ensuing disfigurement is due, not to muscle atrophy as is so often the case in other nerve lesions, but to loss of a fundamental means of emotional expression. The patient with Bell's palsy may tolerate an open watery eye or a tendency to bite his cheek at meals but he is disgusted and ashamed of the grimaces which replace the many subtle movements of normal features. No wonder, then, that everything possible should be done for him.

So far as I know the value of many of the commonly adopted measures for the treatment of an early case of Bell's palsy rests upon the claims of traditional usage and common practice. I doubt whether adequate proof of their worth is forthcoming. Warmth, a mustard leaf, radiant heat, massage and strapping have their advocates and in the majority of instances can do no harm. They may help the patient to maintain his morale. The splintage of paralysed muscles after injury to a nerve is of the utmost importance. It is not equivalent to mere immobilization but is intended to prevent stretching of the paralysed muscles by the action of gravity or by contraction of its antagonists. In facial paralysis the pull of the muscles of the unaffected side is often considerable and stretches the affected muscles. The points of origin and insertion of the latter can be approximated by the use of various types of intra-oral splint or by the familiar hook in the corner of the mouth. But there is something to be said for the criticism that contraction of the muscles of the healthy side of the face will be more likely to stretch the paralysed fibres if the decussation of the orbicularis oris muscle at the corner of the mouth is fixed or actually held back by a hook (Pickerill and Pickerill, 1945). Strapping up of the face, however, even when its sound physiological basis has been explained to a patient, has not, in my experience, been well tolerated. It has been discarded too soon for any estimate of its value to have been reached.

There is another aspect to the management of the early case of Bell's palsy which is important. The theories of the causes and nature of denervation muscle atrophy are numerous. The denervated tissue is certainly not inactive; it is actually hyperexcitable and its fibres exhibit fibrillation. Although the precise mechanism of the atrophy is not known there is now good evidence that it can be reduced by galvanic stimulation of the affected muscles. If from the outset they are made to contract daily they waste little if at all (Gutmann and Guttmann, 1942, and others). Similarly recovery of a muscle during reinnervation is much reduced if the affected part is immobilized (Hines, 1942). Galvanic stimulation of the paralysed facial muscles in Bell's palsy and the encouragement of active movements during the stage of recovery is sound practice. In a neglected case of Bell's palsy one not infrequently finds that galvanic stimulation at first produces no response but after a week or so the muscles may begin to contract and can later be made to do so quite vigorously. There seems to be no doubt that galvanism maintains the affected muscles in a healthier state. If the facial nerve is severely involved so that degeneration takes place and healing must depend on regeneration of the nerve and reinnervation of the muscles, then these processes are more likely to be successful if the muscles have meanwhile been maintained in a favourable condition.

Recovery in most cases begins in a matter of weeks and progresses satisfactorily to a perfect result. But if regeneration of the nerve is necessary then quite obviously signs of returning power will be delayed, progress may be halting and it will vary from case to case. The

result can scarcely be perfect. Nearly a year may pass before facial movements begin to return but two years from the onset of the paralysis recovery may be quite satisfactory. I have witnessed such a course of events yet know little of its incidence. Clearly, to help us decide this vexed question of surgical interference, we need more detailed evidence than this of the natural history of the affection.

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Dr. Philippe Bauwens: *The Electrodiagnostic Aspect of Facial Paralysis*

From the electrological angle, the facial nerve presents a number of curious features which at first glance appear peculiar to it, but which on closer examination can, in certain circumstances, be shown to exist in other peripheral nerve lesions.

Historically, it is interesting to recall that Duchenne of Boulogne made observations on the territory of the VII nerve which led to the publication of his book on "The Mechanism of Human Physiognomy or the Electro-physiological Analysis of Emotions". It was, moreover, the first nerve to be subjected by him to the rigours of electrical stimulation to diagnostic ends.

It is in relation to paralysis that the most striking peculiarities of the facial nerves are observed. Particularly in the case of Bell's palsy do the course and the end-result present these apparent deviations from other peripheral nerve lesions.

As is well known, in a Bell's palsy which remains complete in the third week after its onset, the final issue is unpredictable from clinical examination alone. Electrical investigations yield more information.

Erb evolved his well-known scheme aiming at a classification based on the responses to electrical stimulation carried out two to three weeks after the onset, and from this he claimed that the prognosis could be deduced.

If no alteration in excitability could be discerned, that is to say, if faradic stimulation of the nerve trunk and of the paralysed muscles elicited the same responses as on the unaffected side and the reaction to interrupted galvanic stimulation of the muscles remained brisk, then the paralysis was classed as a *mild form* which would recover in another two to three weeks.

Where reaction of partial denervation was observed, which meant that nerve conduction was decreased and was coupled with diminished reaction to faradic stimulation and sluggish response to galvanic stimulation, the condition was classed as a *moderate form* with a good chance of full recovery in six to eight weeks.

The presence of reaction of complete denervation in all muscles—that is, inexcitability to faradic stimulation and sluggish response to galvanic stimulation—constituted the *severe form* and was considered of grave prognosis. If recovery occurred at all, it might take from six to twelve months and was almost invariably disappointing; contractures and paradoxical facial movements being frequent attendants.

Although this scheme has come in for some criticism, on the score of unreliability, at the hands of subsequent authorities, it is to be noted that these have rarely, if ever, contributed anything of value to supplement it or proffered an infallible scheme as a substitute.

To those who have experience of electrodiagnosis in all fields, it is perplexing, when it comes to a Bell's palsy, to see how differently the findings of a muscle test have to be interpreted and how guarded the prognosis has to be in the presence of complete denervation.

Take the case of a lateral popliteal or radial nerve paralysis of sudden onset and clearly not due to anterior poliomyelitis or severe trauma. Reaction of complete denervation may

be observed, but the prognosis is not unduly grave unless there is some factor which makes it so—as for instance the knowledge that it has been caused by a traction injury or a Volkmann's ischæmia.

To find an explanation for this difference in the outlook in both these cases, it is necessary to examine the processes which might account for Bell's palsy, and compare them with similar conditions in other peripheral nerves.

Bell's palsy is primarily an inflammatory condition of the connective tissues surrounding or supporting the nerve itself—therefore a peri- or interstitial neuritis and paralysis is due to the excessive pressure arising from exudates within the unyielding bony canal just inside the stylomastoid foramen.

The functions of a nerve subjected to pressures of varying degrees and duration are affected in various ways (Fig. 1).

With moderate pressure, it loses its power of transmitting nervous impulses across the section subjected to the pressure, but it does not undergo any lasting histological modifications, nor do the muscles supplied by it do so (Fig. 1A). Moreover, the excitability and conduction of the nerve, distal to the pressure zone, remain unaffected. This local block is termed *neuropraxia*. With greater pressures, local axon discontinuity occurs and if this is maintained for some time, it is accompanied by axon degeneration distally (Fig. 1B). When this *axonotmesis* occurs, not only does the nerve lose its power of conducting impulses, but the muscles supplied by it exhibit alterations in the excitability and response characteristics epitomized as "*reaction of denervation*".

Excessive as well as prolonged pressure can produce even more serious damage by causing the destruction of the connective tissues of the nerve in addition to the axon (Fig. 1C).

Although the reactions to electrical stimulation in this case are in every respect the same as in simple axonotmesis, the presence of a gap between the two portions of the nerve disturbs the repair processes when these are in a position to start.

Regenerating axons have to find their way unguided and unsupported from the central stump to the peripheral one. Even if unhampered by the presence of organized exudates, axons are unlikely to bridge the void and light upon their original medullary sheaths and reinnervate the appropriate groups of muscle fibres.

Again, in the course of repair, some axons may bifurcate several times, thus forming an abnormally large motor unit with a diffuse action—possibly not confined to one muscle.

As the result of work carried out on peripheral nerve injuries during the two world wars, it has been recognized that a nerve lesion in discontinuity—or *neurotmesis*—unless repaired by accurate end-to-end suture, gives rise to neuroma and fibrous tissue formation and any recovery is disappointing (Fig. 1D).

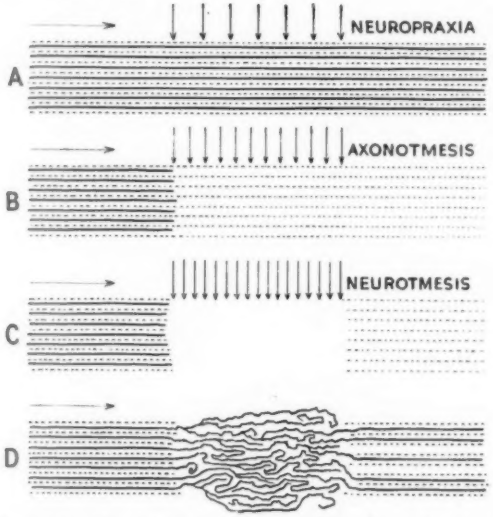


FIG. 1.—Diagram illustrating effect of various degrees and durations of pressure on nerves. (Arrows indicate degree and direction of pressure.)

From the point of view of eventual function, unsatisfactory results could be due to: (*a*) failure to obtain adequate regeneration; (*b*) cross reinnervation; (*c*) motor axons passing down sheaths previously occupied by sensory fibres and vice versa.

The first (*a*) meant that a muscle or a group of muscles was too weak to be functionally effective, or to resist the action of normal antagonists.

The second (*b*) meant that the will to perform one movement produced a different one. This form of dysfunction was revealed by the electromyograph. It was particularly in evidence and disabling in the case of nerves supplying at once two sets of muscles with antagonistic actions—as with the ulnar nerve in the hand where the abducting and adducting muscles of the fingers are supplied by it; or with severe brachial plexus lesions where, for instance, the axons of the phrenic nerve may find their way to the muscles of the upper limb.

The third (*c*) merely spelt waste of regenerating axons.

When traumatic neuromata are formed, irritation phenomena are not uncommon. As demonstrated by Kugelberg the threshold of excitability can be depressed locally to a point where nervous impulses are triggered off spontaneously.

In sensory nerves this causes pain. In motor nerves it produces spontaneous motor unit activity, which does not, however, trouble the patient unduly when it occurs in limb muscles.

The object of this digression into the realm of lesions of other peripheral nerves is to draw attention to some features capable of explaining those anomalies apparently peculiar to the paralysis of the facial nerve.

In facial paralysis of the severe type, recovery is frequently accompanied by contracture and paradoxical or mass facial movements which are identical to the phenomena just described as resulting from neglected nerve injuries with gross anatomical discontinuity. It begs the question whether the severe form of facial paralysis is not, in fact, a neurotmesis as distinct from a simple axonotmesis, with discontinuity occurring in the absence of obvious injury.

Generally the concept of neurotmesis is associated with an injury, but in this instance it would occur as the result of excessive and prolonged pressure over a substantial length of nerve trunk leading to ischæmic necrosis of all tissues in the fallopian aqueduct.

From the diagnostic point of view, the detection of a few intact motor units after two to three weeks in a Bell's palsy therefore becomes most important. If found, the inference is that the pressure inside the bony canal has not reached the degree required to destroy all axons and presumably the connective tissue would then escape gross damage and destruction.

Clinically, the presence of a few intact motor units is not easy to detect as these may be paralysed by neuropraxia. For the same reason, the electromyograph may fail to reveal any motor unit activity on volition, although it may detect a single motor unit which has chanced to escape altogether.

Electrical stimulation of the nerve trunk or the individual muscle motor points with faradic current may not reveal the presence of such intact motor units unless they are in sufficient numbers to produce a visible response in the muscles.

A combination of nerve-trunk stimulation at its exit from the stylomastoid foramen and electromyography should in theory reveal the presence of motor units which have not suffered axon degeneration.

If it were generally agreed that axonotmesis of all nerve fibres carried with it a grave prognosis, and that decompression at an early date was the only treatment which offered a chance of preventing the wholesale destruction of the nerve in the bony canal, then it might be justifiable to subject the patient, in whom other methods had failed to detect undamaged motor units, to this combined test under general anæsthetic.

Management of Bell's Palsy from the Physical Medicine Aspect

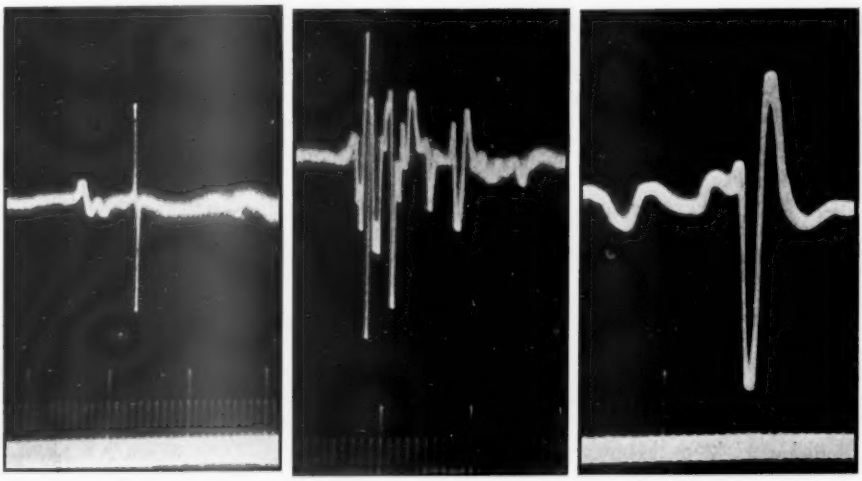
Facial paralysis cases are referred to Physical Medicine Departments for three purposes:

(1) Electrodiagnostic and electroprognostic.
(2) Treatment of the paralysis.
(3) Treatment of the sequelæ.

Early cases, seen within two weeks of the onset, are tested for nerve conduction three times a week. For this, the muscular responses on the affected and the unaffected sides are compared on faradic stimulation of both nerve trunks, with currents of comparable intensities. The rate of deterioration of the response on the affected side—or its absence—is of prognostic value.

(1) *Electrodiagnosis and electroprognosis.*—In cases seen about the third week, the affected side is tested first for nerve conduction, then for the threshold of the muscle response to currents of varying durations. When these threshold values are plotted as a graph, they give the intensity duration curve. The presence of a sluggish response to currents of long duration is noted.

As pointed out, the detection at this stage of one or two motor units which have completely escaped damage or which have escaped with neuropraxia only is most important. As suggested earlier, there might be some justification for administering a general anæsthetic and hunting for unscathed motor units while stimulating the facial nerve at its exit from the stylomastoid foramen. Whereas some motor unit activity on volition or on stimulation means that at least one axon has escaped damage with degeneration, fibrillation potentials at rest (Fig. 2A) mean that at least one motor unit is denervated. The earliest sign of recovery



A B C

FIG. 2.—Electromyographic records of some conditions encountered in facial paralysis. (Time scale in milliseconds.) A. Fibrillation potential (1 millisec. duration) diagnostic of denervated muscle. B. Highly polyphasic potential (15 millisec. duration) occurring in recovering motor units. C. Normal single diphasic potential (8 millisec. duration) of motor unit origin.

after denervation is an electromyographic manifestation with distinctive features (Fig. 2B). It makes its appearance before any movement can be perceived or any change in the type of response to electrical stimulation can be observed. It is easily distinguished from the electrical activity arising from motor units which have escaped damage or which have recovered from a temporary incapacity (Fig. 2C).

(2) *Treatment of the paralysis.*—It may be that it is too often taken for granted that all the damage to the nerve is done at the moment of the onset of the paralysis, whereas this should only be interpreted as an indication that the pressure in the bony canal has reached a pressure sufficient to cause neuropraxia. The further developments of ischæmia, and subsequent thrombosis leading to total necrosis, might possibly be avoided by decompression.

During the early stages of the paralysis, everything must be done to relieve pressure and congestion and to resolve inflammation. Counter-irritant measures—heat, ultraviolet light, &c.; depletion by making use of the anaphoretic effect of the direct current and the decongestive properties of short-wave, particularly when combined with the exhibition of iodine by mouth or injection, appear justifiable methods of treatment.

At later stages, when denervation is established, methods calculated to maintain the motility and mobility of muscles as well as the circulation should be instituted pending recovery. In order to prevent muscle stretching and to minimize disfigurement, a small plastic-coated hook can be fixed to the appropriate tooth so as to fit into the corner of the mouth.

With recovery, exercises and self-massage are substituted for the more passive treatments.

(3) *Treatment of the sequelæ.*—Contracture is probably not produced or aggravated by excessive treatment as thought hitherto. It is probably an expression of irritability of the nerve over the repaired section. If it is due to impulses originating spontaneously and rhythmically over this portion of the nerve and being translated into muscle contractions, then any measure calculated to raise the threshold of excitability should be tried.

Encouraging results have been obtained at St. Thomas's Hospital with prolonged therapy with calcium chloride ionization to the ear and affected side of the face, and administration of a combination of calcium and calciferol by mouth. The improvements obtained have been subjective at first and eventually objective.

No therapy is at present of any avail for massive facial movements and paradoxical movements. This is not unexpected when it is appreciated that they are due to regenerating axons branching or reinnervating the wrong motor unit or even interacting with one or more neighbouring axons. The patient should, however, be made to exercise in front of a mirror in order that he may realize the extent of the movement produced and attempt to control this within the limits of his capacity to do so.

Much of the therapy suggested may appear based on very slender grounds, but one thing is certain, and that is that a sufferer with a facial paralysis will insist on treatment. If one does not treat him someone else will, and as a large percentage of these cases recover spontaneously, claims for cures will be made from the wrong quarter and for the wrong reasons. Moreover, a form of treatment which maintains a patient's morale, is not harmful and may do some good by maintaining muscle action, is not entirely without its *raison d'être* or justification.

Dr. Bauwens showed photographic records of wave form obtained by means of the electromyographs (Fig. 2).

To illustrate cross innervation, he showed a patient who had a brachial birth palsy and in whom action potentials related to the respiratory rhythm could be demonstrated electromyographically in the biceps. These stopped with respiratory arrest and were easily distinguishable from the action potentials obtained in the biceps on attempted flexion of the elbow.

Section of Experimental Medicine and Therapeutics

President—Professor G. W. PICKERING, M.A., M.B., F.R.C.P.

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SOME APPLICATIONS OF THE NEWER ANTIBIOTICS

The Scope of the New Antibiotics

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A brief review was given of the development of chemotherapy from the laboratory studies of Ehrlich, Domagh, Fleming, Dubos, Florey, Waksman and others. The clinical application of chemotherapeutic substances, including the antibiotics, had led to improved methods in the laboratory diagnosis of various infections (examples were cited) and had fostered closer co-operation between clinician and laboratory worker.

THE clinician, if he is to obtain the best results with the increasing range of new antibiotics, needs the help of the laboratory in regard to the nature and drug sensitivities of the infecting organism, the choice of drug, and the optimum dosage (amount, spacing and duration of treatment) to give adequate blood levels and ensure bacteriological as well as clinical cure of the infection. In deciding on the choice of drug for an infection in any particular patient, he must carefully consider a number of factors. These include the effectiveness of the drug to deal with that particular infection, its toxicity, the ease of administration, and the cost to the patient or the community.

(1) *Effectiveness.*—It is first essential to determine the causative agent of the particular infection. In diseases like pneumonia, meningitis and cystitis, there is a wide range of infecting agents which respond to different antibiotics or to none at all. For example, pneumonia may be caused by a variety of bacterial pathogens, of which the pneumococcus may respond best to sulphonamides, the staphylococcus to penicillin or aureomycin, and Friedländer's bacillus to streptomycin; or it may be due to non-bacterial agents of which the psittacosis virus, the Rickettsia of Q fever and the virus of primary atypical pneumonia may all respond to one or other of the new antibiotics (aureomycin, chloromycetin or terramycin) whereas infection with the influenza virus will be unaffected by any of them. In meningitis, sulphonamide is still the drug of choice for cerebrospinal fever; penicillin, intrathecally as well as systemically, is best for the other acute coccal infections; streptomycin for *H. influenzæ* and tuberculous meningitis; and perhaps polymixin for pyocyaneus infections. It is still too early to say whether some of the newer antibiotics will be more effective than those at present used for the treatment of the acute pyogenic forms of meningitis.

At the same time as the infecting organism is being isolated, its sensitivity to a range of chemotherapeutic substances should be determined. This can most readily be done by the use of small paper discs impregnated with suitable concentrations of the respective drugs and planted on the culture plate. A zone of inhibition of growth round a particular disc will indicate that the organism is sensitive to that drug and the extent of the inhibition will give some guide to the degree of sensitivity (Thompson, 1950). It is essential to test sensitivities of bacteria as soon as possible after isolation, particularly with organisms like the staphylococcus which may already be resistant

to penicillin, and the coliform group or *H. influenzæ* which quickly acquire resistance to streptomycin. However, infection with a staphylococcus that shows some resistance to penicillin *in vitro* may still respond to massive doses of the drug, since the response will depend on the numbers and activity of penicillinase-producing staphylococci in the lesion.

[Charts were shown to indicate the response to 4 mega units of penicillin per day of cases of staphylococcal pneumonia and septicæmia due to penicillin-resistant strains.]

On the other hand, an antibiotic may be very active against an organism *in vitro* but have little effect in the treatment of infection with that organism. For example, the typhoid bacillus is very sensitive in the test tube to polymixin but this drug has no therapeutic effect in typhoid fever. Incidentally, polymixin is also very active *in vitro* against *Ps. pyocyanea*, and surface infections with this organism, e.g. infected burns or chronic ear discharges, often respond to local applications of the drug.

It is often difficult for the individual clinician to assess the effectiveness of a new drug in a particular infection since his own limited experience may have led him to be either too optimistic or too pessimistic. Assessment of the therapeutic value of the antibiotic drugs by a system of controlled clinical trials in a number of co-operating centres has yielded very satisfactory results in this country; as, for example, in determining the optimum dosage of penicillin in subacute bacterial endocarditis; or in the treatment of different forms of tuberculous infection with streptomycin. Similar trials with aureomycin and chloromycetin are now being sponsored by the M.R.C. Antibiotics Clinical Trials Committee in pertussis, infantile enteritis, pneumonia and other infections. It may be noted that these controlled trials can best be organized when supplies of the drug are limited, and in this respect we may be more fortunate than our American cousins.

(2) *Toxicity*.—The toxicity of a drug may show itself in a variety of forms. It may be locally irritant to the intestinal mucosa causing nausea, vomiting and diarrhœa. This local irritation, which occurs with aureomycin and PAS, may be overcome by giving the drug in a bland fluid like milk or combining it with an antacid or giving smaller doses more frequently. There may develop allergic reactions to the drug itself or to associated impurities, with rashes, sometimes of considerable severity, as the commonest manifestation; or there may be sharp reactions of sensitized tissues to bacterial products resulting from the rapid autolysis of the endogenous bowel and respiratory flora when chloromycetin or aureomycin is administered—a kind of Herxheimer action. Spink *et al.* (1948) have noted increased pyrexia in patients with undulant fever within the first day or two of commencing treatment and they recommend that in this disease the initial dosage should be small and then gradually increased.

There may be a direct toxic action on selected tissues. Streptomycin affects the auditory nerve, Gray (1950) has found that chloromycetin may induce muscle fatigue by some effect on muscle metabolism, and aureomycin may have a stimulating effect on the growth of young animals although this latter action may be related to changes in the bowel microflora and the synthesis of vitamin B_{12} (Stokstad *et al.*, 1949; *see also Lancet*, Editorial, 1950 (i), p. 912). An indirect toxic action may also result from the temporary elimination of the normal respiratory and intestinal flora with a replacement flora of abnormal coliform bacteria and yeasts. There may be complaint of sore throat with stomatitis, glossitis and oral fissuring; in the female, in whom these symptoms are more common than in the male (Harris, 1950), there may also be vaginitis with vulval and anal irritation. How far these symptoms are due to the secondary bacterial flora and how far to deficiency of vitamin B complex resulting from elimination of the normal intestinal flora is still undecided, although Harris claimed to reduce their incidence and severity by the simultaneous

administration of vitamin B. A tendency to bleeding, also noted by Harris in some of his patients, may be associated with vitamin K deficiency.

The development of drug resistance is another hazard in antibiotic therapy. This phenomenon, which has lately attracted much attention in the laboratory as a genetic problem, is a frequent occurrence with streptomycin treatment, is rare in penicillin therapy with the exception of staphylococcal infections, and is said to be uncommon with the new antibiotics although we have some evidence of its occurrence in chronic urinary infections treated with chloromycetin and aureomycin. The answer to this problem may well be the use of combined therapy, particularly with streptomycin against which bacterial resistance develops so readily. A combination of streptomycin and PAS in the treatment of pulmonary tuberculosis has already been found to hinder the emergence of streptomycin-resistant tubercle bacilli, and other suitable combinations, e.g. streptomycin and sulphonamide in urinary infections, should be used where indicated.

(3) *Cost and ease of administration.*—While cost must be disregarded where the life of a patient is at stake, the relative cost to the community of different methods of treatment which are equally effective deserves some consideration. Thus a drug which can be given by mouth to a patient in his own home will cost much less than a drug that has to be given by repeated injections in a hospital ward. In this way aureomycin, which is readily absorbed from the gut, may become preferable to penicillin which is poorly absorbed, for the treatment of staphylococcal and streptococcal infections, although it should be noted that oral therapy with penicillin, preferably given on an empty stomach and in doses five times that of the parenteral dose, has proved effective in pneumonia, gonorrhœa and other infections. Again, the new aqueous suspensions of procaine penicillin are easy to inject and require only one dose a day, while in the treatment of tuberculous infections streptomycin is now given in single daily doses or even at less frequent intervals.

The new antibiotics, aureomycin, chloromycetin and terramycin, when assessed on the criteria of effectiveness, toxicity, ease and cost of administration, score high marks. Their range of activity is much wider than that of penicillin or streptomycin for they are almost equally active against both Gram-positive and Gram-negative bacteria. Aureomycin seems to be the more effective drug against the Gram-positive coccal infections (staphylococcal, streptococcal and pneumococcal), while chloromycetin is the drug of choice in enteric infections. Both are effective in undulant fever and tularæmia, and both have proved useful in chronic urinary infections that have not responded to sulphonamides or streptomycin. These drugs are also effective against Rickettsial infections (typhus, scrub typhus, Rocky Mountain spotted fever, and Q fever) and against the psittacosis-granuloma group of viruses. They may be useful in trachoma, herpes zoster, mononucleosis and amœbiasis but are ineffective against the poxes and such common virus infections as the common cold, influenza, measles, mumps, and rubella. They are relatively free from direct or indirect toxic effects; they are effective when given by mouth at six- to eight-hourly intervals; and the emergence of drug-resistant strains is a rare occurrence. The disadvantages are that they are bacteriostatic rather than bactericidal and therefore require the active co-operation of the host's tissues in eradicating the infecting organism. Relapses in typhoid, undulant fever and Rickettsial infections treated early have been unduly common with these drugs, and there may be a fertile field for combined chemotherapy and immunotherapy. Because of their very bitter taste, their administration to young children who cannot swallow the usual size of 250 mg. capsule has created a pharmaceutical problem. This difficulty may be overcome by the prescription of the drugs as enteric-coated granules. Lastly, the therapeutist and pharmacologist must diligently watch for any chronic toxic effects of drugs that would seem to owe part of their effectiveness to their ability to diffuse into the tissue cells themselves.

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Chloromycetin in the Treatment of Typhus and Typhoid

By R. LEWTHWAITE, D.M., F.R.C.P.

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I WISH to describe a piece of medical investigation carried out by a group of workers in a tropical country, Malaya. The project to undertake investigation in typhus and typhoid with chloromycetin was initiated by Dr. Joseph E. Smadel, Scientific Director of the Virus and Rickettsia Division of the United States Army Post-Graduate and Research School, Washington.

Scrub typhus is unknown in the United Kingdom, save for laboratory mishaps. It is a distinctive component member of that group of typhus diseases, one or the other of which occurs in each of the five continents. They may be briefly classified as louse-borne, flea-borne, tick-borne and mite-borne, the last named of which is my first subject this evening. It is scrub typhus, identical with the classical tsutsugamushi disease of Japan. The former synonym supplanted the latter for obvious reasons when the disease flared up amongst the Allied Armies in the recent Japanese War in regions that are best indicated by an arc drawn from Northern Assam through Burma, Ceylon, Malaya, Indonesia, Indo-China, Queensland, New Guinea, Formosa, and Japan. In pre-war days it had not greatly obtruded in medical statistics. Only those who worked or sought recreation in jungle contracted it. During the war it emerged from comparative obscurity to menacing notoriety; 30,000 cases occurred in British, Australian and American forces, of whom some 10% died and 25% were after lengthy convalescence invalided home. It is inoculated into man by one or other of a group of mites, *Trombicula akamushi*, *Trombicula deliensis*, &c.; the causal organism is the *Rickettsia tsutsugamushi*; the mite lives on the wild rat, and on some birds. Essentially a disease of mites and rats, the ebb and flow of jungle warfare necessitated man going into the haunts of this disease, and, in consequence, he frequently supplanted the rat as the host, and so contracted the disease.

During the war, much intensive investigation had been concentrated on it: Counter-measures are threefold, anti-rat, anti-mite, and anti-Rickettsial. Early in the war against the Japanese, investigations by Australian and American scientists, working independently, culminated in the demonstration that mite-poisons could be successfully used in the field by the impregnation of clothing, and that dibutyl phthalate or benzyl benzoate surpassed all others. According to the Australian Army Authorities, by this measure alone, scrupulously applied, the incidence of the disease could be reduced by 75%.

Anti-Rickettsial counter-measures made little headway during the war. Vaccines proved inconclusive. Recently, however, by another line of approach an astonishingly successful advance has been made in the development of the two antibiotics, chloromycetin and aureomycin. The use of the former will receive precedence in this narrative, since the author has greater familiarity with it, and it was used almost exclusively in the Malayan work.

The drug originated from a mould, *Streptomyces venezuelæ*, isolated from a sample of soil taken in Venezuela and sent to Dr. Paul R. Burkholder, a botanist at Yale. He found it to have anti-bacterial activity, and therefore passed it to the Research Division of Messrs. Parke, Davis & Co., of Detroit, who found filtrates to be active. From these the active principle was isolated in pure crystalline form: on its being found

in the laboratory to affect many viral and Rickettsial agents it was passed to Dr. Joseph E. Smadel, Director of the Virus and Rickettsia Division of the Research and Graduate School of the United States Army Department, for extended trials. Laboratory investigation soon revealed its curative value against the major Rickettsial infections when studied in laboratory mice and embryonated eggs. Since no significant signs of any toxicity due to the drug were observed, Dr. Smadel decided to proceed at once to human therapy.

The wartime inroads of scrub typhus into casualty lists and into morale were fresh in the memory; new foci of incidence had revealed themselves in Malaya; civilian and soldier alike were frequently "at risk" when traversing secondary jungle. The Institute for Medical Research, Kuala Lumpur, had long been studying scrub typhus, and to it Dr. Smadel turned for laboratory space and collaborative effort in a projected evaluation of chloromycetin.

The protocols of the laboratory experiments in Washington were undoubtedly encouraging, especially in animals and chick embryos treated late in the infection, and I, the then Director of the Institute, had no hesitation in accepting Dr. Smadel's proposal to bring a hand-picked Scrub-Typhus Research Unit. A British Scrub Typhus Research Unit of three scientists, led by Dr. J. R. Audy, had already begun a field study of mites and vectors; and it seemed clear that progress must accrue.

Chloromycetin in the therapy of scrub typhus.—In Washington plans went rapidly ahead. During four months of preparation Dr. Smadel and two colleagues visited Mexico, and succeeded in obtaining 5 cases of epidemic (louse-borne) typhus, and 2 cases of murine (flea-borne) typhus. All responded promptly to chloromycetin therapy, including one elderly patient treated as late as the eighth day of the febrile reaction. The omens for the success of the drug in scrub typhus seemed thereby to be all the more favourable.

In March 1948 the American Scrub-Typhus Research Unit arrived in Singapore by a special army plane, in which were carried frigidaires, incubators, hot-air ovens and the like, together with two jeeps and the world supply of chloromycetin—1 lb. in weight. Twenty-four hours after arrival at the up-country capital of Kuala Lumpur, the treatment of two soldiers, one British and one Malay, was begun by Dr. Theodore E. Woodward, the specialist physician of the Unit. Both soldiers were severely ill; in one, at least, the prognosis was doubtful, high fever of six or seven days' duration, a rash, a dermal lesion, lymphadenitis, severe headache and a marked toxicity constituting a very harassing infection.

The drug, chloromycetin, was given by mouth in the tablet form supplied by the makers; it was of the "fermentation" type. The scheme of dosage was to give an initial "loading-dose" of 4 grammes (16 tablets) based on a ratio of 50 mg./kg. body-weight. It was followed by decreasing doses every three hours as progress dictated. After the first twenty-four hours it was noted that the patients, though still febrile, showed no increase in toxicity. After forty-eight hours the temperature fell to normal, and remained so permanently. The drug was continued for six or seven days in the first few cases. Thereafter every case of scrub typhus received the drug; in all, the same dramatic defervescence and loss of toxicity were the outcome.

Favoured by an outbreak on a near-by rubber estate that yielded 40 cases, and by a trickle of cases incurred by the troops as a result of jungle training, a series of some 60 treated cases was rapidly amassed. Trial of different dosages made it clear that treatment for one day only was adequate—a loading dose of 4 grammes, followed by 0·25 gramme every three hours until a total of 6 grammes had been given. In later cases gelatin capsules of the drug supplanted the tablets.

We had thus witnessed an extraordinary event, namely, the immediate cure of a disease, long intractable to any specific therapy, achieved by the oral administration of a handful of tablets or capsules.

The next phase of the investigation was ushered in by the receipt from Washington of 11·25 grammes of a "new type of chloromycetin". Two patients (Gurkha soldiers) with a syndrome of considerable severity were readily secured. Both were treated for one day only, one receiving 5·5 grammes and one 4 grammes. In both, within forty-eight hours, the temperature fell to normal and toxicity vanished; uninterrupted convalescence ensued. The "new type" of the drug was chloromycetin prepared by synthesis in the Research Division of Messrs. Parke, Davis and Company, Detroit, by Rebstock and her colleagues (1949). Raistrick (1949) has appraised this signal achievement, and his account should be consulted by those in quest of detail. Thereafter drug prepared by either method was used.

Another phase in the investigation of scrub typhus was the testing of chloromycetin as a prophylactic agent. No difficulty was experienced in obtaining adequate numbers of volunteers by advertisement in the daily newspapers. An infected field on a rubber estate near-by, with small areas adjacent to it, ensured that there would be no lack of mites if the climatic circumstances were favourable. Five highly organized field trials were carried through. Selected sites were chosen according to the tally of the vector mites on exposed white rats. Large consignments of white mice were flown to Kuala Lumpur from Melbourne, London and Manila for the detection of Rickettsiæmia in the volunteers at various stages of the exposure to infection.

Two of the field exposures were outstanding in the data procured. In the first of them, 17 of 24 untreated controls contracted the infection after the usual incubation period of eleven to eighteen days; they were thereupon admitted to hospital and their infection terminated by chloromycetin. In the corresponding treated group of 22 cases, 1 gramme of the drug was given daily for the last nine days of exposure and the succeeding twelve days; all remained well until the thirty-first day, when a quiet confidence that Rickettsiæ had been eliminated from each was rudely shattered by the onset of scrub typhus in 12 of the 22. The disease had been merely suppressed by the daily drug, on the cessation of which the usual incubation period began and ushered in the complete clinical syndrome of the disease.

The second field exposure, suitably modified in procedure, was more successful. Exposure was shortened to six days only; the two test groups received chloromycetin orally in once-weekly doses of 4 grammes for four and six weeks respectively, some starting on the sixth day and some on the tenth day from the beginning of exposure in the field. Of the 31 volunteers thus exposed, only one developed the disease sufficiently to warrant admission to hospital. Some of the others showed an incipient clinical syndrome (with Rickettsiæmia) towards the end of the intervening weekly periods between doses; but it was effectively eliminated by the impending dosage of the drug, so that all of them remained ambulatory. None of the 30 developed the clinical disease after the completion of the prophylaxis.

Emanating from these experiments in human prophylaxis was an unexpected and (at the time) somewhat disconcerting finding. Patients who contract the disease in the course of their ordinary occupational duties seldom reach the hospital ward and receive a diagnosis before the fifth to sixth day of the clinical syndrome; in these, whether treated with chloromycetin or not, relapse does not occur. It was therefore puzzling to note that many of the volunteers who, since they were under daily observation, could be treated on the first to third day after onset, developed one or more relapses. They responded promptly to another course of the drug.

Mode of action of chloromycetin in scrub typhus.—Smadel (1950) has discussed at some length this aspect of the investigations. He concludes that chloromycetin is not rickettsiocidal but is rickettsiostatic; that the drug does not *per se* eliminate the organisms. In the naturally infected patient in whom treatment with the drug is perforce delayed until about the seventh day, the multiplication of the Rickettsiæ has stimulated the development of antibodies to a degree that, with the aid of the

suppressive active of the drug, enables the bodily defences to control the infection permanently. In contrast, in the case of volunteers treated earlier in the infection, the bodily defences have lacked the stimulus of a comparable degree of multiplication of Rickettsiæ, and are inadequate, in spite of the administration of the drug, to control the infection effectively.

The treatment of typhoid fever.—In the differential diagnosis of scrub typhus, the physician has to consider leptospirosis, murine (flea-borne) typhus and typhoid fever. It was inevitable, therefore, that in the series of scrub typhus cases studied by the American Unit some that ultimately proved to be typhoid should be treated with chloromycetin. The eventuality was indeed welcomed, and the design of the investigation expanded accordingly. Reports giving interim results are now appearing in the literature, and should be consulted for detail (Woodward, Smadel *et al.*, 1948 and 1950), (Smadel, 1950). It was soon evident that chloromycetin of the fermentation type, given orally as tablets, was effective therapeutically; for by the second or third day the toxicity was rapidly diminishing, and the temperature reached normal on the fourth day of treatment. These responses occurred whether treatment was begun early in the illness or late.

At the outset of the investigation Dr. Woodward, the physician of the Unit, gave an initial dose of 3 grammes, followed three-hourly by 0·5 or 0·25 gramme, with a gradual reduction of dosage on succeeding days. The first series received approximately 18 grammes spread over eight to nine days. Of these, a number relapsed after an average of eleven days from cessation of therapy; a further course of chloromycetin reproduced the mitigating features described above as resulting from the first treatment; second relapses occasionally occurred. It was clear that the treatment should be extended. As more of the drug became available, a small series of patients received the following dosage: an initial dose of 4 grammes, followed by 1·5 grammes at twelve-hour intervals during the four days of fever, then 1·5 grammes (single or divided) for the next seven days, followed by 1 gramme daily until the completion of fourteen to eighteen days of treatment. An alternative scheme designed to obviate relapses has been an initial period of treatment of five days (dosage as above), then five days without the drug, followed by a second period of treatment in dosage identical with the first. The synthetic type of drug was equally as effective as the fermentation type.

The chronic typhoid-carrier state has so far failed to respond to chloromycetin therapy; there is no reason to think that it has been increased, however. Smadel (1950) has reported that in concentrations of a few gamma per c.c. of culture media the drug will inhibit growth, but that even a thousand gamma will not kill the organisms. He would regard the balance between the host, the parasite and the immune mechanism as already established, and unlikely to be materially affected by a transient suppressive drug.

The Malayan series of typhoid cases was 44 in number; the only death was in a youth admitted to hospital in coma, and later found to be perforated. Since then many similar series have added to the now very considerable tally of series which have been reported from various countries, most of them recording the same favourable results. There can be no doubt that, on present evidence, this drug, now made by synthesis, has greatly blunted the menace of typhoid fever.

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Chloromycetin in Infantile Gastro-Enteritis

By James M. Smellie, O.B.E., M.D., F.R.C.P.

Infantile gastro-enteritis still takes a heavy toll of infant life and in 1947 was responsible for approximately one-eighth of the deaths of infants under the age of 12 months.

Treatment, at the present time, is essentially symptomatic and consists of endeavours to correct the dehydration and electrolytic disturbances produced by the excessive fluid and salt losses. Sulphonamides and penicillin have proved to have been of real value in some cases but, in general, the results obtained have not been very satisfactory, particularly in those diarrhœas of non-specific or unknown origin. Preliminary reports with streptomycin were promising but further experience has been disappointing.

During recent months chloromycetin has been used at the Birmingham Children's Hospital in the treatment of 27 cases. The ages of these patients have varied from 4 weeks to 9 months but 23 were under the age of 6 months. As the supply of this drug was limited, its use has been restricted to infants who were seriously ill and whose survival was in jeopardy. The clinical condition of 17 was so critical that at the time treatment was started they were intolerant of oral feeding and intravenous alimentation was required to combat the dehydration and associated symptoms.

The dosage of chloromycetin has been 75 mg. per pound (165 mg./kg.) of body-weight per day, given at three- or four-hourly intervals. The average duration of treatment has been ten to twelve days, in no case was the period shorter than seven days and in a few was continued for a fortnight.

Every patient, with the exception of a single case to which I shall refer presently, has shown appreciable clinical improvement shortly after the introduction of chloromycetin. This observation has been repeated so consistently that it is not easy to accept as a coincidence. As a rule improvement took one or two days to manifest itself and, thereafter, clinical anxiety was relieved and progress uneventful. The majority of these infants had no parenteral infection but in a few the disease was complicated by a superadded infection outside the alimentary tract. In most instances the lesion was in the upper respiratory tract and consisted of an otitis media or a pharyngitis; one had a staphylococcal septicæmia. All these responded to chloromycetin as satisfactorily and as promptly as those whose infection was limited to the gastro-intestinal tract.

In a few of the infants the responses to chloromycetin appeared to be dramatic, as illustrated by the following two cases:

Case I.—E. C. On admission, this 4-month-old infant was very dehydrated and semicomatose with a desperate and critical toxæmia. He had been treated in another hospital for several days with intravenous therapy, sulphonamides and penicillin without response. Shortly after admission his condition deteriorated still further, he had a sharp hæmatemesis followed by convulsions which persisted for several hours and his chances of survival appeared very remote. He was given a blood transfusion, all oral feeding stopped, intravenous therapy re-started and chloromycetin begun. Intravenous fluids were continued for three days and nothing given by mouth except sips of water. Within twenty-four hours his improvement was spectacular and his subsequent convalescence was rapid and uneventful. He was discharged cured on the twentieth day (Fig. 1).

Case II.—B. M. This infant, aged 7 weeks, was admitted suffering from a pyopneumothorax. Soon afterwards she developed a severe and explosive diarrhœa. Ten days' treatment with intravenous fluids, sulphonamides, penicillin and streptomycin failed to arrest the progress of the disease and her condition had become critical. Here, too, the response to chloromycetin was prompt and impressive. Within twenty-four hours her temperature, pulse and respiration had returned to normal and she began to regain weight rapidly (Fig. 2).

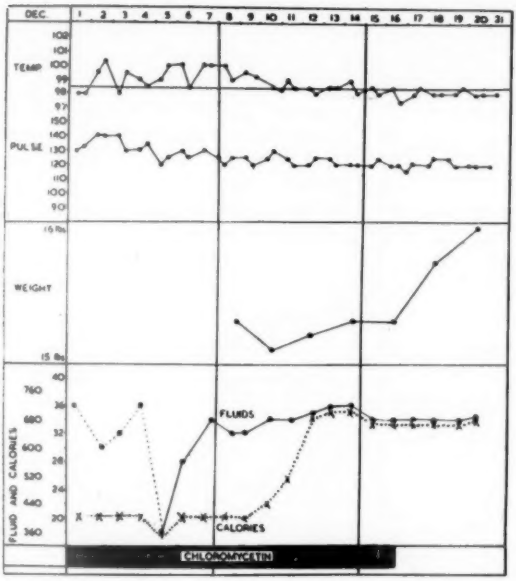


FIG. 1 (*Case I*).—E. C., aged 4 months.

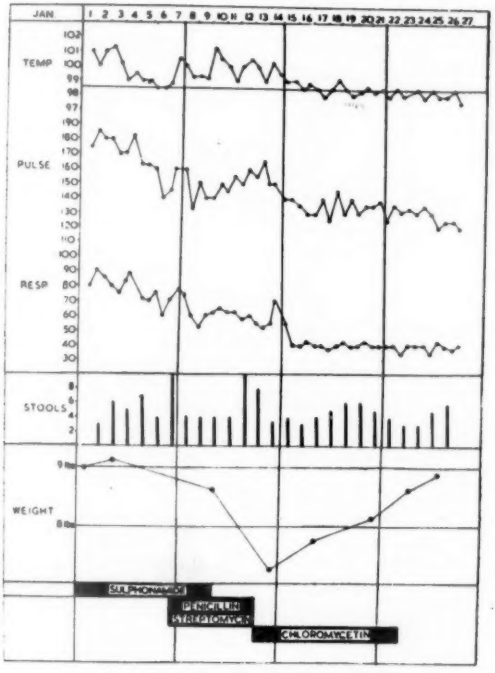


FIG. 2 (*Case II*).—B. M., aged 7 weeks.

Careful attention has been paid to any untoward reactions or complications which might be ascribed as due to the drug. Soon after it was taken into use an impression arose that the incidence of sore buttocks was higher in infants having chloromycetin, and this remains a lingering question. Case I, however, to which reference has already been made, appears to refute this doubt. When he was admitted he had a severe excoriation of the buttocks and this healed as quickly and as satisfactorily as could have been anticipated, whilst he was still having chloromycetin. Another lesion that has attracted attention is stomatitis which was present in a few cases. Whether this was due to chloromycetin or to thrush (*Monilia albicans*), which is not destroyed by this antibiotic, has not yet been decided. At the time with which I am concerned there was an unusually high incidence of thrush in infants being admitted to hospital. Lastly, 2 cases of cutaneous eruption have been observed. One was a generalized papular urticaria and the other an allergic type of dermatitis largely confined to the region of the buttocks and the groins. Whilst notice must be directed to these cases, I am unable to say whether chloromycetin did or did not play any part in their production.

Only one death has occurred. This infant was admitted suffering from extensive scalds of the buttocks, and presently developed acute toxæmia and severe gastro-enteritis, which failed to respond to sulphonamides, penicillin or chloromycetin.

In conclusion, it must be emphasized that the utmost caution is necessary in the assessment of any treatment of infantile gastro-enteritis. Epidemics of the disease vary widely in intensity and severity with fluctuating mortality rates not only in different localities but also at different times in the same locality. Any comparison, therefore, with results obtained at one time with those of some other time previously is very liable to lead to erroneous and misleading deductions and conclusions.

When due attention has been paid to all these limitations, and to the absence of any directly comparable control cases, a firm impression remains that the results obtained with chloromycetin are more encouraging and more promising than have been achieved with other chemotherapeutic or antibiotic substances.

Dr. E. N. Allott:

Twenty-one cases of typhoid fever were admitted to the Brook Hospital, London, from the S.S. "Mooltan" and were treated with chloromycetin. In all cases the clinical response was very satisfactory. There was complete disappearance of symptoms by lysis over a period of forty-eight to seventy-two hours and the patients thereafter remained well. However, a large proportion of the patients subsequently showed a relapse which responded equally well to chloromycetin.

The relapses occurred, in the very great majority of cases, at between eleven to fifteen days after the cessation of chemotherapy, i.e. approximately the normal incubation period for the disease. Some of the patients were treated by the orthodox Woodward-Smadel regime for periods up to fifteen days, others were treated with a short intensive course of 20 grammes in forty-eight hours, but the frequency of relapses and the time of relapse seemed entirely unrelated to the duration of treatment in the initial attack. The only toxic symptom with the larger doses was temporary blurring of vision.

In view of these findings it is suggested that in future treatment on the following lines might be considered: A short course of treatment until the patient has become apyrexial and then a further short course of treatment, starting about nine or ten days after cessation of the first course, to prevent relapse.

President—Professor R. A. McCance, M.D., Ph.D., F.R.C.P., F.R.S.

[*October* 10, 1950]

The Present Status of Cortisone and ACTH in General Medicine

By Philip S. Hench, M.D.

Dr. Philip S. Hench, of the Mayo Clinic and Professor of Medicine at the University of Minnesota (Mayo Foundation), addressed a meeting of the Experimental Medicine Section on "The present status of cortisone and ACTH in general medicine". The meeting, to which members of the Sections of Endocrinology, Medicine, and Physical Medicine were invited, crowded out the Barnes Hall and the proceedings were relayed to the West Hall. The chair was taken by the President of the Section, Professor R. A. McCance, who was accompanied by the President of the Society, Lord Webb-Johnson.

Dr. Hench projected a film showing the results of cortisone or ACTH in a number of cases of rheumatoid arthritis studied by himself and his colleagues Drs. E. C. Kendall, C. H. Slocumb and H. F. Polley. It revealed the striking improvement in the posture and movements of patients and the disappearance of joint pain on pressure following a few days' use of the hormones, also the return of symptoms when, without the patient's knowledge, the hormones were withheld and a neutral substitute given.

At the close of the lecture Professor McCance expressed the thanks of the assembly to Dr. Hench. He said that the lecture had demonstrated how much could happen in eighteen months of medical research, and he wondered what further achievement there would be to record if they made a date with Dr. Hench in eighteen months' time. They had to thank not only Dr. Hench himself, but the Past President of the Society, Sir Henry Dale, who had got Dr. Hench to come, and the Nuffield Foundation which had made his visit possible.

Dr. Hench began his lecture with the statement that about 28 crystalline compounds and an amorphous residue had been separated from the adrenal cortex. One of these, Kendall's compound E, renamed cortisone, had been found to possess marked physiological potency. The anterior lobe of the pituitary secreted several hormones, one of which, the adrenocorticotropic hormone (ACTH) had the power to stimulate the adrenal cortex to pour forth its own products. Cortisone, according to some, was only one (though perhaps the chief) of the products which the adrenocorticotropic hormone stimulated the adrenal cortex to secrete; others took the view that cortisone, or a cortisone-like substance such as compound F, was the only hormone made by the adrenal cortex.

Differences Between Cortisone and ACTH

Several differences between cortisone and ACTH had to be noted. The absorption and distribution of ACTH was rapid; hence it must be given three or four times a day at first; that of cortisone acetate was slow, and one daily injection usually sufficed. ACTH, being a protein, sometimes produced foreign protein reactions; cortisone, being a crystalline substance, induced no such reactions. An important difference was that cortisone and ACTH were not, clinically or physiologically, equal milligramme for milligramme. Apparently 100 mg. of ACTH might stimulate the production of 200 or more mg. of cortisone; so that doses of about 40 mg. of ACTH were comparable with those of about 100 mg. of cortisone.

Within recent months it had been found that both agents not only influenced a few relatively rare endocrine conditions, but might affect rather profoundly many diseases which appeared to be non-hormonal and to have no connexion with the

pituitary or adrenal gland. In this broader sphere both were found to have anti-rheumatic properties, first in rheumatoid arthritis and then in acute rheumatic fever. Their suppressive effect on the "collagen" diseases then became apparent. They were also found to possess marked anti-allergic activity and to have a limited influence on certain blood dyscrasias.

The value of these agents as research tools could not yet be assessed, nor their merits as therapeutic agents finally predicted, but it appeared to be sufficiently established that a surprising variety of inflammatory reactions of widely different nature and causation could be suppressed, at least temporarily, by their administration.

Rheumatoid Arthritis

Dr. Hench here recapitulated the investigations which had led up to the first administration of cortisone in a case of rheumatoid arthritis in September 1948 and then the use of ACTH in such cases in February 1949. Improvement in the symptoms and signs of rheumatoid arthritis generally developed within two or three days, sometimes within a few hours, after daily injections of cortisone or ACTH were started. A diminution first of subjective and later of objective phenomena occurred, with a sense of well-being and increased psychomotor activity. Sedimentation rates went down and hæmoglobin concentrations increased. Electroencephalograms revealed changes in the alpha waves in patients during the administration of these hormones. The potency of these hormones when given alone having been established, orthopædists had begun to study their effects in conjunction with non-surgical procedures for correcting resistant flexion contractures.

Some patients had now received the hormones more or less continuously for several months. Relief of symptoms usually continued for as long as the hormones were given, but afterwards relapses had occurred, usually within one or two months of cessation of hormonal usage, though certain patients retained much, sometimes almost all, of their relief for several months without the hormones.

Rheumatic Fever

The acute manifestations of rheumatic fever had been quickly abolished by adequate doses of these hormones—apparently more quickly and consistently than by salicylates or other previous remedies. Fever, acute polyarthritis, tachycardia, and "toxæmia" usually disappeared promptly within a few days. Symptoms of acute rheumatic carditis were lessened or abolished—at least in some cases—and there were reductions in cardiac size. Within the limits of short follow-up studies, no definite signs of new, or increased old, carditis had developed from the acute attacks which were suppressed by the hormones.

It was the opinion of Dr. Hench and his colleagues, among them the cardiologists Drs. Arlie Barnes and H. L. Smith, that the hormones apparently did not "cure" the rheumatic condition even in those cases in which the abolished symptoms did not return on the stoppage of the hormonal injections; nor, probably, did they shorten materially the natural course of the acute rheumatic state or protect the rheumatic susceptible from his next attack.

Acute rheumatic fever developed when the latent rheumatic state of the susceptible was activated by the presence of an unknown irritant, commonly related to certain hæmolytic streptococcal infections. To this acute irritant certain tissues of the patients reacted sharply to produce the characteristic clinical picture of the disease. The acute phase of rheumatic fever might be defined as the time during which the unknown irritant was present or during which the tissues reacted to this irritant.

Cortisone and ACTH seemed to buffer the tissues against the irritant. The exudative reactions quickly subsided, and there was ground for thinking that even the proliferative reactions might be suppressed. If this was so, maximal protection could only be provided by continuing to give the hormone for the full duration of the acute rheumatic state (six to twelve weeks). After the acute state had passed the patient should be shielded by chemoprophylaxis (oral penicillin or sulphonamides) against the dangers of subsequent streptococcal infections.

Other Conditions

Dr. Hench then passed in review a large number of conditions in which the hormones had been used with varying results. In a few cases of osteoarthritis the symptoms had been moderately or markedly relieved; in others not at all. Acute gouty arthritis had been rapidly subdued. Three patients with pulmonary tuberculosis (without arthritis) had shown marked subjective improvement when given ACTH, but the pulmonary lesions in one case progressed during its use and in another increased after discontinuance. In two patients with proved tuberculous arthritis (without pulmonary lesions) cortisone brought about a decrease of articular symptoms and sedimentation rates, but tuberculin and other tests remained positive.

In disseminated lupus erythematosus some of the clinical features were usually markedly suppressed by cortisone or ACTH, but the incidence of adverse hormonal effects appeared to be higher in this disease than in most others. In some cases psychic aberrations, convulsive seizures, retention of fluid, and transient hypertension developed. Articular lesions with psoriasis had been more responsive to the hormones than had the skin lesions, which often seemed to require higher doses.

Cases of chronic ulcerative colitis had been studied. In a case with arthritis, cortisone, given for thirty-five days, induced a complete articular remission, also a symptomatic remission of the colitis which had lasted for seven months.

The hormones appeared to be strongly anti-allergic. A rheumatoid patient, given cortisone, was coincidently relieved of his hay fever. Marked remissions in perennial asthma or bronchial asthma with status asthmaticus had also been reported. Post-hormonal remissions lasted from one week to five months. A severe case of infantile atopic eczema, a few cases of urticaria or other skin reactions from sensitivity to penicillin, gold salts, or other drugs, and cases of allergic rhinitis had also been relieved.

One of the most promising fields of usefulness for these hormones was in acute and subacute inflammatory diseases of the eye. Marked and prompt results had been reported in uveitis, scleritis, iridocyclitis, and the like. Until recently hormones had been given intramuscularly for these ocular conditions, but now studies in local application of cortisone in eye drops or in ophthalmic ointment were being made by Drs. Olson, Peterson *et al.* at the Ford Hospital and by Drs. Henderson and Hollenhurst at the Mayo Clinic.

At the Mayo Clinic a few patients with periarteritis nodosa had had prompt subjective relief with the use of cortisone or ACTH. The local and systemic symptoms in two cases of cranial arteritis were apparently controlled by cortisone. In certain cases of leukæmia temporary remissions of varying duration and degree had been induced by a first or sometimes by a second course, but subsequent courses had been increasingly ineffective. In cases of nephrosis a beneficial diuresis with loss of œdema might be induced. In certain neurologic and psychiatric conditions (acute

poliomyelitis, acute multiple sclerosis, amyotrophic lateral sclerosis, myasthenia gravis, catatonia, schizophrenia) results had been negative or inconclusive.

Mode of Action of the Hormones

The physiological effects of cortisone and ACTH, Dr. Hench continued, appeared to be non-specific, by which he meant that if large enough doses were given for a sufficient length of time an effect could be demonstrated in almost everyone, normal or otherwise. Nevertheless, the ability of the hormones to ameliorate markedly almost the whole symptom-complex of certain diseases appeared to be group-specific. In affording this relief they did not kill germs or remove "unknown irritants", and therefore they did not *per se* cure the diseases the symptoms of which they modified so profoundly. But in some unknown manner they appeared to provide the susceptible tissues with a shield-like buffer against a wide variety of irritants. How they accomplished their anti-rheumatic effect was, to use a Churchillian expression, "a riddle wrapped in a mystery inside an enigma". They did not extinguish the fire, nor, carpenter-like, repair the damage, but they provided an asbetos suit in which the patient, like Shadrach, Meshach, and Abed-nego, walked unscathed in the furnace. If the protection was not discarded until the end of the natural duration of the "fire" the patient remained well.

"Side Effects"

The hormones were in general well tolerated, especially if given for only a few weeks; but sometimes a variety of undesirable effects might occur, some of them of little importance, others presenting certain hazards. Fairly frequent effects were mild irritability, initial retention (generally mild) of sodium chloride and water, mild hypertrichosis, acneform eruption, and "round face". Rare or rather rare side effects were transient reduction of carbohydrate tolerance, hypopotassæmic hypochloræmic alkalosis, major alterations of psyche, and spontaneous fractures in elderly osteoporotic persons. Owing to its potential effects cortisone or ACTH should be used with caution in hypertensive cardiovascular disease, diabetes mellitus, tuberculosis, old rheumatic carditis with decompensation, latent or frank psychoses, and senile osteoporosis. As a result of intensive studies side effects were now assuming a less prominent position; they were features to be respected, but not to be feared.

To obviate these side effects, and also to overcome the disadvantage of limited supply and high cost, an intensive search had been made for other steroids, more or less related chemically to cortisone. Except for compound F (not yet synthesized) the search so far had been fruitless. About 50 of these "mysteroids" (as Hollander of Philadelphia calls them) had been tested for clinical activity in rheumatic and other patients, and none had given significant results. As several of them differed from cortisone only in a single configuration, it appeared that the chemical structure of cortisone was remarkably specific.

Plan of Administration

Each of the responsive diseases might need a different plan of administration, and dosages might vary from case to case and from time to time in the same case. Children seemed to require about the same doses as adults with the same disease. Fairly large suppressive doses were required at first for a few days or weeks, and then, when the condition was well under control, smaller doses could be given for a short time in certain conditions and for prolonged periods in others. In the acute crisis of disseminated lupus erythematosus or severe rheumatic fever and carditis the initial period doses might be, for example, 300 mg. for the first day, and 200 mg.

daily until improvement was definite. The basic policy must be to provide the greatest symptomatic relief possible consistent with the avoidance of significant side effects.

Current Developments

Although the method for producing cortisone had not been shortened, as a result of further investigation some of the steps in the partial synthesis had been made less costly and productive of greater yields. The price had now dropped to 50 dollars per gram, and Merck's supplies were now sufficient to make cortisone available in limited amounts to all approved American hospitals, with growing supplies available for foreign medical centres. In the development of ACTH the pituitaries of whales were being collected and utilized by Scandinavian scientists.

Attempts had also been made to find some material which, when given with cortisone, would enhance the effect of doses too small to produce side effects.

On the development of compound F, which, according to certain data, was the ultimate product of the adrenal cortex rather than compound E (cortisone), Dr. Hench said that this substance until recently could be obtained only by extraction from adrenal glands. No method for its synthesis had so far been developed, but the development of a method for the biological conversion of compound F from substance S (Reichstein) had just been announced.

A patient with severe rheumatoid arthritis was given in May 1949 an oral preparation of a highly concentrated adrenal cortical extract. The patient received about 20 capsules daily (100 mg.) of a mixture of compounds E and F. The response was excellent and essentially the same as with intramuscular injections on the same patient. The sedimentation rate rapidly became normal and the patient almost completely free from symptoms.

In June last, at the meeting of the American Rheumatism Association, excellent preliminary results were forthcoming with Merck's cortisone given orally to four patients by Dr. Richard Freyberg of New York, and these results had been confirmed at the Mayo Clinic. Cortisone tablets had now been given to about 25 rheumatoid patients at the Mayo Clinic with very satisfactory results. It was very encouraging to find that cortisone was effective when given by mouth in doses approximating to those which were effective when given intramuscularly. Dr. Hench added, however, that the administration of such preparations must be carefully controlled by the physician, or serious abuse of the hormone might result. The tablets for experimental use were made from small amounts of sterile cortisone taken from the main supply, and none would be generally available in this form for some time to come.

In conclusion Dr. Hench said:

"As cortisone and ACTH have been found to influence profoundly many different cells and tissues of the body so they are having a marked effect on widely diversified fields of biological and clinical research. New vistas for investigation have been revealed. New concepts are being developed in the spheres of clinical physiology, clinical pathology, and clinical medicine. Much remains to be learned about ACTH and cortisone, about their mode of action, and the optimal method for their administration, especially in chronic diseases such as rheumatoid arthritis. The remark is still true, that this is not the beginning of the end of the problem of rheumatic diseases, but perhaps it is the end of a beginning. But so much progress has been made in recent months that the limited application of these hormones as therapeutic measures for at least certain acute conditions appears properly to be impending."

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Section of Epidemiology and State Medicine

President—W. H. BRADLEY, D.M., M.R.C.P.

[*April* 21, 1950]

DISCUSSION ON POLIOMYELITIS FOLLOWING INOCULATIONS

Professor F. M. Burnet (*Director of the Walter and Eliza Hall Institute, Melbourne*): The investigations carried out in Victoria during 1949 by Dr. B. P. McCloskey have recently been reported (1950 *Lancet* (i), 659). The data on the relationship between the onset and site of paralytic poliomyelitis and the fact of a preceding injection of an immunizing agent, which I have to present, are wholly derived from McCloskey's work, and include with his permission a supplementary series of cases investigated subsequent to the completion of the paper mentioned.

When the probability of a relationship had been recognized a careful study of the history in regard to immunization or injection of any sort was made for all persons reported as suffering from poliomyelitis. The records obtained consisted essentially of statements covering the time and site of any injections received within three months of the onset of illness, the agent used for injection, the date of onset of poliomyelitis and the intensity of paralysis in each limb. The two important points that have emerged from McCloskey's analysis of the data are, first that the great majority of the cases associated with injections in the preceding three months occurred within thirty days of injection, and, second that there was an equally striking localization of severe paralysis to the limb inoculated nearest to seven days before the onset of illness.

The association was much more striking with injections of pertussis or combined pertussis-diphtheria antigens than with diphtheria toxoid (usually APT), but this may have been in part due to the fact that the first group were of relatively homogeneous ages (9–33 months) while those receiving diphtheria antigens were older and less homogeneous. Tables I and II provide a clear picture of the essential character of the findings. In Table I, 55 patients are tabulated according to the type of antigen administered and the period elapsing before the onset of paralytic illness. The figures are divided into two groups, those in which the limb last injected was paralysed and those in which it was not. The concentration in the first month of cases showing paralysis in the relevant limb is immediately obvious.

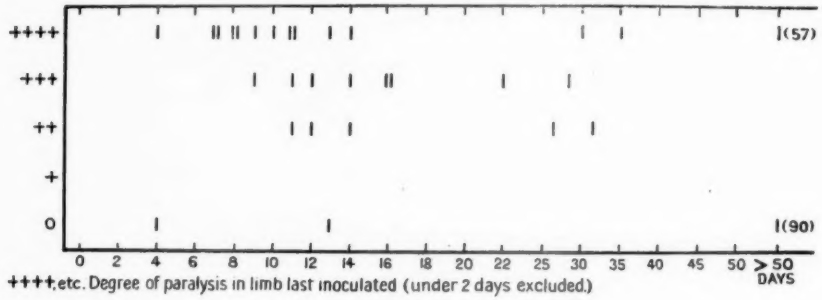
TABLE I.—TIME ELAPSING BETWEEN LAST INOCULATION AND ONSET OF POLIOMYELITIS IN 55 PATIENTS

		Incubation period		
Inoculum		0–30 days	31–60 days	61–90 days
A.	P	7	0	0
	P–D	20	4	0
	D	4	0	1
B.	P–D	2	0	2
	D	8	5	2

A. Children showing paralysis of the last injected limb.
B. Children showing no paralysis of the last injected limb.
P. Pertussis vaccine. P–D Combined pertussis-diphtheria antigen.
D. Diphtheria antigen.

Table II is a graphic illustration of the distribution of "incubation" periods in relation to degree of paralysis in the relevant limb for the homogeneous group receiving either pertussis or combined antigens. The concentration of incubation periods between seven and fourteen days is striking but there are 4 cases with the characteristic localization to the injected limb in which an incubation period of over a month is evident.

TABLE II.—DISTRIBUTION OF "INCUBATION" PERIODS IN CHILDREN UNDER THREE YEARS, GIVEN PERTUSSIS OR P–D



There can be no doubt that there is a significant relationship between the injection of a pertussis or combined antigen and the subsequent appearance of moderate to severe paralysis in the limb injected. On the Victorian figures there is no more than a strong probability that diphtheria APT injection has a similar less intense effect.

The importance of such an occurrence in regard to all immunization programmes needs no stressing. It is urgent that the situation should be closely analysed in order to judge what action may be needed to prevent future occurrences of similar type, and the greater part of this contribution is devoted to discussion of the possible pathogenesis of the condition. It is accepted as being established by McCloskey's figures that, in a significantly large number of young children, inoculation of antigen was followed by severe paralysis of the injected limb appearing ten or twelve days afterwards. In the absence of immunization these children would either have escaped paralysis or shown much less evident paralysis in the limb concerned.

The vital points that need elucidation are the localization of paralysis to the last injected limb and the characteristic incubation period.

The localization of paralysis must indicate that in some way the local injection has influenced the anterior horn cells of the corresponding region of the cord. The only means by which that influence could be conveyed is via the nerves in the vicinity of the deposited antigen, and three types of agent passing along neural paths (in a broad sense) to the spinal cord can be envisaged—poliomyelitis virus, a toxic non-viral substance or some type of nerve impulse. This offers a suitable basis for discussion of the possible types of pathogenesis.

(1) The possibility that the virus had been introduced by the needle at the time of the injection was fully discussed in Melbourne particularly in the light of what is known of syringe transmitted hepatitis. It was concluded that such transference of poliomyelitis virus could only occur under most exceptional circumstances, and that the possibility of its being responsible for an extensive series of cases could be excluded completely.

(2) If poliomyelitis virus circulating in the blood could be removed from the blood stream in the inflamed area surrounding the antigen deposit; if it could multiply in this region and thence pass to the spinal cord by the neuronal path, an explanation of the incubation period would be available. Such a view, however, ascribes characteristics to the virus which have never been demonstrated. Only if a new type of strain with very unexpected properties is concerned would this hypothesis be tenable.

(3) The passage of a toxic substance, derived either from the deposited antigen or from the resulting tissue reaction by the neuronal path to the corresponding region of the spinal cord, must be considered. As with all hypotheses not involving movement of virus from the site of the antigen deposit, it must be assumed that the motor cells of the cord are rendered unduly vulnerable to attack by poliomyelitis virus reaching the central nervous system.

(4) The presence of the antigen deposit and the surrounding inflammatory reaction may produce nervous stimuli of some sort which influence the anterior horn cells, perhaps in a way analogous to the effect of excessive muscular exercise. Any such process would have to be one taking some days to reach the intensity needed to induce the changed vulnerability of the motor cells. The suggestions may be made that active irritation either by a local antigen-antibody reaction, or by the development of a fibrous tissue response might be delayed for the period required.

The decision between these hypotheses may come in part from experimental work, but my chief justification for presenting them is to provide a basis for further study of the conditions under which paralytic sequelæ to inoculation occur in children. There are many possibly relevant facts to be collected and analysed. Perhaps the most important task is to define the conditions under which pertussis or combined pertussis-diphtheria immunization is not followed by paralysis. In the course of extensive controlled trials of pertussis immunization in this country no related cases of poliomyelitis have been observed. In America where a large proportion of infants are immunized and poliomyelitis is common and closely studied, no cases have been reported and the impression amongst some competent authorities is that the association must be at least very rare.

What are the factors responsible for these differences? Aspects that need consideration are: the incidence of poliomyelitis in the times and places concerned: individual peculiarities of the prevalent strain of poliomyelitis virus: the age at which immunization is performed, and the technique of inoculation—is intramuscular injection more potent in this respect than subcutaneous for instance? The nature of the inoculum may also turn out to be important. Is the impression that pertussis vaccines are much more potent than diphtheria toxoid preparations actually justified? Only an analysis of such data from regions in which there is no evidence of paralytic sequelæ as well as from those in which the association has been observed will allow the formulation of a sound administrative policy.

In the present state of knowledge I feel that we are bound to cease pertussis immunization for any period in which there is a high incidence of poliomyelitis in the community concerned. Diphtheria immunization is so important to the community that only very clear evidence of the occurrence of harmful sequelæ should be allowed to interfere with the policy of universal immunization. If the whole situation is adequately investigated I feel hopeful that in a year or two we shall have defined the dangers sufficiently to continue with full confidence those immunization procedures which are becoming an essential part of our public health measures and indeed of our general community life.

Dr. Dennis Geffen (*Medical Officer of Health, St. Pancras Metropolitan Borough*) referred to the investigation that he had made in London during 1949.

In September two cases of poliomyelitis had been notified to him by Dr. Susan Tracy, occurring in children, aged 10 months, who had been immunized with a combined vaccine within the previous two weeks. An immediate investigation showed that 6 such cases had occurred in St. Pancras and 6 in Islington.

In St. Pancras 75% of the children were immunized with the combined reagent, whilst in Islington more children were immunized with pertussis vaccine alone than with the combined reagent.

In all cases the paralysis had affected the limb of injection, but in one or two, different limbs were concerned, a condition which could be accounted for by other reasons, as, for instance, in one case the giving of penicillin in the gluteal region during the incubation period.

In conjunction with the Medical Officers of Health of London boroughs, he had investigated the position throughout the whole of London. At the time of his report the number of notified cases of poliomyelitis in London since the beginning of the year was 359, and in children under 5, 182. 30 children under 5 had developed poliomyelitis within four weeks of being immunized against diphtheria and/or whooping cough, the paralysis affecting in particular the arm of injection. In 21 cases a combined vaccine had been used, in 8 cases APT and in 1 case, whooping cough vaccine.

Dr. Geffen called attention to the fact that he and Dr. McCloskey, working 12,000 miles apart, had come to similar conclusions and published figures almost identical.

He was of the opinion that it was unfortunate to mix so well tried a prophylactic injection as APT with a vaccine against pertussis, which although promising, had yet to be proved. It would be most unfortunate if as a result of the association between poliomyelitis and the combined vaccine, the faith of the public was shaken in connexion with immunization against diphtheria.

Of the 145 children who had not been recently immunized but nevertheless developed poliomyelitis, the site of paralysis was as follows:

Paralysis of legs only	47
Paralysis of arms only	14
Paralysis of legs and arms	12
Paralysis of face only	4
Paralysis of multiple groups of muscles	16
Polio-encephalitis	1
No paralysis	11
Site of paralysis not ascertained	40
	145

In 7 cases paralysis had ensued within a month of immunization but did not affect the limb of injection.

Dr. Geffen was satisfied that there was an association between the activation of paralytic poliomyelitis and immunization with the combined vaccine. He did not know yet, however, what association there was in connexion with the use of APT alone. The figures, though suggestive, were not large enough to state definitely that coincidence could be ruled out.

The recovery rate was about 50%; more or less the same as for those cases of poliomyelitis which were not associated with any inoculation.

Dr. Geffen had communicated with experts on the epidemiology of poliomyelitis in America but had been informed that, so far, no association between immunization and poliomyelitis had been recorded. This might be due to differences in the immunizing reagents used in America and England. Alternatively, it is quite possible that further investigations would show a correlation. It had been his experience in writing to his colleagues in England that when once their attention was called to the possibility, it had not been long before they had discovered a set of conditions similar to those he had recorded in London.

If Dr. McCloskey's findings and his caused the medical profession to pause and think for a moment there was at least this to be said, that as a result of the two epidemics in England of 1947 and 1949, a line of research had been opened which might help in discovering the cause of paralysis in those who were carrying the virus of poliomyelitis.

Professor A. Bradford Hill : In the statistical inquiry that Dr. J. Knowelden and I have carried out, with the assistance of the Medical Officers of Health of administrative areas widespread in England and Wales, particulars were obtained of 410 children under the age of 5 years, each having been previously notified and confirmed as a case of poliomyelitis with onset in the latter half of 1949. For each of these children information was sought on (*a*) the site of paralysis (if any) produced by the illness, and (*b*) the child's full history, from birth, of prophylactic inoculations (excluding vaccination against smallpox). A comparative group of children of the same age and sex distribution and from the same areas as the poliomyelitis cases was also obtained, so that it might be seen whether the poliomyelitis group had been inoculated more frequently than the general run of children. This comparative group was constructed of either children notified as suffering from measles or children born at the same time as those with poliomyelitis, each such child being very carefully paired with a corresponding poliomyelitis case. All the poliomyelitis cases could not be successfully paired but by such means 164 "control" children were obtained. The full inoculation histories of these children were also sought.

Looking first at the poliomyelitis group it was found that the distribution of paralysis over the limbs was quite abnormal in the children who had had an injection of an antigen in the month preceding the onset of their illness. In children not previously inoculated, or without any recent injection, paralysis occurred equally in the right and left arms and paralysis in the legs was between two and three times as frequent as paralysis in the arms. On the other hand, in those inoculated within the preceding twenty-eight days paralysis was more frequently observed in the left arm than in the right arm, and paralysis in the arms was more frequent than paralysis in the legs. There was no indication that an injection at least three months previous to the onset of poliomyelitis influenced in any way the site of paralysis. For injections between one and three months previously the data were few but it is probable that here too there were no effects of inoculation upon paralysis. Thus the effects were limited to children of recent injection. In these children, too, it was apparent that the limb which was the site of a recent inoculation—whether arm or leg—was more frequently a site of paralysis than was observed in children not recently inoculated. Thus of 36 children under 2 years of age and inoculated within twenty-eight days of the onset of their illness, 29 (81%) had paralysis in the limb of inoculation (as the only site or as one of the sites of paralysis). Of 65 children of the same ages but inoculated more than twenty-eight days earlier only 13 (20%) had paralysis in the limb of injection (clearly the limb of inoculation must sometimes

coincide with the limb of paralysis merely by chance). This paralysis in the limb of injection was found to have followed recent inoculations with APT and inoculations with the combined APT and pertussis vaccine. Very few figures were available for pertussis vaccine alone but one case of paralysis was noted to follow such an injection. Division by age showed that children under 2 years of age and also between 2 and 5 years were affected.

Comparison of the poliomyelitis cases with their controls showed that rather more of the former had been inoculated at some time or other. Division by time revealed that this excess lay wholly in inoculations given within the month preceding the onset of the attack of poliomyelitis, a result which suggests that inoculation had brought some children into the paralysed group who would not otherwise have been there.

The enquiry thus showed that in this country, as in Australia, inoculation and poliomyelitis have sometimes been associated. It was not designed to measure the actual risk of such an event occurring or the relative risks with different antigens.

Abstract of paper published in the *British Medical Journal* 1950 (ii), 1,

Dr. A. H. Gale : All of us must have been impressed by the evidence which has been brought forward to show that there is some association between a recent inoculation and the site of paralysis in poliomyelitis. There are many things that we do not know about this association but it seems to me that, from the practical point of view, the most important thing to find out is how great is the risk of converting a potentially abortive or non-paralytic case into a paralytic one. This risk is a most difficult one to assess as it probably varies enormously at different times and in different places.

The following table may be of interest as an indication of the size of the problem:

England and Wales: *Age-group* 0–4. *Year* 1949.

A.	Estimated mid-year population 0–4	3,701,000
B.	Number immunized against diphtheria 0–4	528,812 (incomplete)
C.	Notifications of poliomyelitis (including polioencephalitis) 0–4	2,163
D.	Number of double events reported (various sources)	56

B is incomplete because there was some delay in the making of the arrangements for completion of records of immunization by general practitioners. It does not include immunization against pertussis alone nor does it include injections given for other purposes. D is derived from many sources — the London cases, Professor Bradford Hill's enquiry, the hospital survey which is not yet complete but has already covered 1,470 cases in age-groups 0–4, and reports from a number of doctors. In the year 1949 in addition to the 56 reports which seem to refer to true double events there have been 22 which were doubtful either as regards site or time relationship or for some other reason. In addition to these, 8 reports have been received where there seemed to be no relationship. Thus 86 reports have been received in the year, of which 56 seemed to relate to true double events. I do not think that one can draw any conclusion from these figures but suggest that they leave an impression that, considering the large number of children immunized, the double event is very uncommon.

As a footnote I should like to mention that the number of deaths from diphtheria in England and Wales in 1949 was 85 as compared with an average of 2,528 annually in the four years 1938–41.

Dr. G. M. Findlay said that certain experiments carried out on the effects of non-specific shock in mice infected with the Lansing strain of poliomyelitis might be of some interest in connexion with the problem of the effects of inoculation on poliomyelitis. The Lansing strain of poliomyelitis was infective for mice only when injected directly into the brain. After intravenous injection of the virus and intramuscular injection of pertussis vaccine and diphtheria toxoid (APT) there was no increased permeability in the blood-brain barrier. In the same way the intramuscular injection of virus following the intramuscular injection of pertussis vaccine and toxoid into the same area did not increase the tendency for virus to localize in the central nervous system. When the same quantity of Lansing virus was injected intracerebrally into a batch of mice of the same strain, age, and sex the mice developed symptoms in from three to twenty-one or more days. If Lansing mice were injected intracerebrally and two or three days later a non-fatal dose of pertussis vaccine and toxoid, toxoid alone or TAB vaccine were given intravenously the mice developed symptoms of paralysis and died more rapidly than those which had received only the Lansing virus intracerebrally. The differences between the figures for shocked and normal mice were statistically significant.

It would seem that once poliomyelitis virus has found its way into the central nervous system of mice non-specific shock tends to bring on symptoms of paralysis and death more rapidly.

Mr. B. Benjamin: When the attention of the London County Council was drawn to the possibility of attacks of poliomyelitis being associated with inoculations, we realized that no investigation of such a serious problem would be of value unless it was controlled. Uncontrolled investigations only exploit the anxiety of the public without providing that scientific justification which our social responsibility requires us to seek. We therefore gave as much help as we could to the careful investigations carried out under the direction of Professor Bradford Hill. At the same time we made a few calculations ourselves. The complete inoculation history of every notified case of poliomyelitis in 1949 was obtained from local records. In order to obtain controls for comparison, I asked the health visitors in London for a random selection of infants on their records. I did not tell them the purpose of my investigation and there is no reason to believe that the list of names which they presented was not representative of the normal infant population. I obtained the inoculation history of these infants also. I then matched every case of poliomyelitis with a control infant of the same age and sex and compared their inoculation histories as at the date of notification of the poliomyelitis cases. The results are shown in the table:

Health Division of County	No. of poliomyelitis cases paired with same number of controls	Cases with inoculations during four weeks preceding notification of "paired" case					
		APT		APV		Combined Diph. and Wh. C.	
		Polio.	Control	Polio.	Control	Polio.	Control
1	60	4	3	—	—	—	—
2	70	1	—	—	—	5	1
3	37	2	—	—	—	3	3
4	13	—	1	—	—	7	4
5	20	1	—	1	—	—	2
6	11	—	—	—	1	2	1
7	34	1	3	—	1	3	—
8	28	—	—	—	—	3	—
9	39	1	—	1	—	1	—
Total	312	10	7	2	2	24	11

Taking the County as a whole, there is in the poliomyelitis cases no statistically significant excess of recent inoculation with diphtheria toxoid alone, or whooping cough vaccine alone, but there is a statistically significant excess of recent inoculations with combined antigen. These figures suggest that in a few cases poliomyelitis has been associated with inoculation with the combined antigen, but they do not measure the risk of an inoculated child being attacked by poliomyelitis. To measure this risk would mean comparing the incidence of poliomyelitis in inoculated and uninoculated infants and would not be easy to do because of difficulty in assessing the proportions of these two groups in the population and especially in making allowances for the differences in their age constitution.

We have made a few rough calculations but we prefer not to give figures at this stage. The tentative conclusion we have reached is that for diphtheria toxoid there is no significant addition to the risk of contracting poliomyelitis, but that for the combined antigen there is an increase in the risk of infection during an epidemic period. The number of inoculations with diphtheria toxoid in London, 1949, was twice as great as the number of inoculations with combined antigen and we feel that if there had been any increased danger with the diphtheria toxoid alone, the numbers are great enough for it to have emerged to a significant extent.

Dr. J. K. Martin: I first became interested in this problem while working in the Outpatient Department at Great Ormond Street in the summer of 1948. Initially I saw 2 cases presenting with a flaccid paralysis of one arm who had received inoculations in the same limb within the previous three weeks. Subsequently, I collected 17 such cases which are recorded in greater detail elsewhere. At the same time, with the help of the Ministry of Health, hospital clinicians and with access to the poliomyelitis files of two large hospitals, I was able to peruse the records of about 100 cases, the data from which served to confirm the findings in my own small series. Reports of similar occurrences have now been produced in Australia.

The age of these patients reflected that at which inoculations are commonly given, i.e. mostly between 6 months and 2 years. The sexes were equally distributed. The incubation period was usually between seven and twenty-one days. Paralysis occurring more than twenty-eight days after inoculation was not considered to bear any causal relationship. In the majority there was a clear history of constitutional disturbances preceding the onset of paralysis. In some seen at the onset neck rigidity and pyrexia were present.

The onset of a flaccid paralysis was sudden and when it affected an arm, the shoulder girdle muscles and muscles of the upper arm and the extensors of the wrist were involved. The wrist flexors and small muscles of the hand usually escaped. The corresponding tendon reflexes were absent. No sensory loss was found. In those cases which recovered, the wrist extensors and certain muscles of the shoulder girdle became active within a few days. The biceps and then the triceps groups were contracting within two to three months. The deltoid and spinati were the last to recover and took up to a year to achieve full function. In the legs a complete flaccid paralysis sometimes occurred, but on the whole the muscular distribution was more variable. The quadriceps and anterior tibial muscles were most commonly affected. The degree of recovery in all types was not constant but good function could be expected in something approaching 50% of cases.

Of the investigations carried out on a few of the cases seen early enough in the disease to be of value, the findings in the cerebrospinal fluid were the most significant. The raised protein and increase in cells (chiefly lymphocytes) were comparable to the findings in poliomyelitis.

Of the materials used for inoculation, in cases taken from all sources available including many of Dr. Geffen's, there were 69 in which APT had been used alone, 37 following combined APT and pertussis vaccine, 3 pertussis vaccine, 1 TAF, 1 TAB and 3 after penicillin. Cases occurred after the first, second, or third injections. Nothing akin to serum sickness was seen. The materials were supplied by at least 6 different manufacturers. In some cases the actual material used, or a similar batch sample, was returned to the manufacturers for examination. Culture proved to be sterile and no untoward effects were noted when injected into animals.

The epidemiology of this condition is of interest because the maximal incidence occurred in the summer and early autumn, and closely followed the seasonal incidence of poliomyelitis. There is evidence also to show that cases tended to occur in areas in which the incidence of poliomyelitis was high at the time.

The points in favour of this paralysis being due to poliomyelitis are the seasonal incidence, the constitutional symptoms, the changes in the cerebrospinal fluid and the absence of sensory findings. It is still necessary, however, for cases to be examined sufficiently early to allow of lumbar puncture, and particularly to prove the diagnosis by isolation of the virus by animal inoculation. If this diagnosis is subsequently proved beyond all doubt, the questions which remain to be answered are the exact part which inoculation plays in its production and also the incidence. That inoculation probably plays an integral part is shown by the overwhelming frequency with which the limb affected has been that into which the injection was given. In cases of poliomyelitis following inoculation, an arm alone was affected in 70% and in 10% one leg. For most poliomyelitis epidemics the corresponding figures are 7% for an arm and 32% for a leg. Further, the right arm is more frequently affected than the left, whilst in post-inoculation cases the left arm is affected at least four times more frequently than the right. With regard to the incidence it was found in studying nearly 200 poliomyelitis hospital records, that for every 100 cases about 8 had occurred within a month of inoculation. Obviously the incidence must be determined more accurately and it must be shown that such an incidence is higher following inoculation than in the population at risk, before effective prophylactic measures can be considered. Nevertheless with such facts as are already at our disposal it might be well to consider the advisability of confining inoculations to periods of the year when poliomyelitis is not prevalent. Any action likely to harm the inoculation campaign must be deprecated before the fullest facts are available.

Dr. L. Reti said that paralysis of a limb could be caused by a blockage of acetylcholine synthesis or by a structural damage through chemical and/or enzymatic means when an entry is secured to the motor nerves and neurons either by enzyme inhibitors, like Mg-ions and Mg-compounds in high concentration, or by antienzymes, like Chastek-paralytic enzyme (thiaminase) or by analogous nucleoproteins from micro-organisms.

He suggested that severe local reaction caused by intramuscular injection offers such an entry at the myoneural junction to the motor nerves and neurons, where enzymatic synthesis of acetylcholine takes place.

The ATP-system present there is engaged in acetylcholine synthesis and, functioning with (1) apoenzymes, (2) co-enzymes, carboxylase, and metallic activators, is sensitive to higher Mg-concentrations (Mg anæsthesia).

Nucleoproteins, which are functioning as apoenzymes of the injected micro-organisms, or of other adjuvants present in the host, may be activated in the traumatic muscle tissue by the released myosin, creatine phosphate, adenylic compounds, and Mg-ions. These foreign nucleoproteins are assumed to have been acting in the analogous ATP and carboxylase systems of certain micro-organisms, and by their nature of apoproteins would then determine "type specificity" of a newly formed enzyme, functioning on their own pattern, and causing structural damage to the motor nerves and neurons.

Dr. F. O. MacCallum: Stools from several children from different areas of London who developed paralysis within three weeks of prophylactic inoculation have been injected into monkeys. So far, monkeys inoculated with stools from three of these children have developed a disease similar to experimental poliomyelitis in the monkey and at post-mortem lesions pathognomonic of infection with poliomyelitis virus were found in their central nervous system. This finding of poliomyelitis virus in the stools of these children does not prove that their disease was poliomyelitis but the strains isolated from the above cases will be used for experimental investigation of the problem. Material from fatal cases occurring after inoculation has not yet been available for study.

Professor Wilson Smith: Professor Burnet mentioned the possibility that poliomyelitis, following inoculations of diphtheria and whooping cough prophylactics, may be caused by a mutant strain of poliomyelitis virus. Although he considers that this is not a very likely explanation, it seems to me that it is a point of fundamental importance upon which further evidence should be readily obtainable. There is certainly nothing inherently improbable in the hypothesis. We do know that in the case of the influenza viruses, sudden mutations occur and, moreover, that modern means of rapid transport may result in an apparently new mutant strain appearing almost simultaneously in very widely separated localities. For example, the dominant epidemic strains of 1947, differing from all previously isolated strains, appeared in several different countries within a relatively short period.

The crucial point in the present connexion is whether, in fact, the U.S.A. has experienced post-inoculation paralytic poliomyelitis in the same way as Australia and this country. If not, as the information so far available suggests, the case for the mutant virus hypothesis would be greatly strengthened, although it would still remain, of course, merely one of several alternative explanations.

Dr. Philip Evans: The most probable explanation for the absence of these cases from the American literature is that they have not been looked for particularly. When Dr. Martin encountered some at Great Ormond Street in 1948 he was able to discover others by examining the records of children treated for poliomyelitis in earlier years.

Professor R. Cruickshank said that as one of the combined diphtheria and pertussis antigens used during the Melbourne outbreak of poliomyelitis was a British preparation containing alum, and as the use of a similar combined antigen, or APT alone, seemed in this country to be associated with post-inoculation poliomyelitis, it may be that the British diphtheria and pertussis prophylactics are more likely to produce an irritant lesion at the site of inoculation than is the case with North American prophylactics in which alum is not used so much.

Dr. H. Stanley Banks referred to the outbreak of 1947 in which year there were more poliomyelitis cases than in 1949, and also probably as much immunization. Yet very few "double events" (paralysis following recent inoculation in the same limb) were then reported. He had observed two such events among his own cases in 1947, although no systematic enquiry was made into a history of immunization among poliomyelitis cases admitted in that year. This was done in 1949 and six double events were recorded. He suggested that lack of awareness might have been a factor in the apparent low incidence of double events in 1947.

Dr. H. J. Parish: There are other neurological sequelæ of pertussis vaccination, viz. fatal encephalopathies. Fortunately these complications have been extremely rare in this country. Have any cases been reported in Australia, and what are Professor Burnet's views on the pathogenesis? Is a latent virus activated by the vaccine, as may be the explanation of poliomyelitis after inoculations?

Professor F. M. Burnet in reply: From what has been said I feel that the conditions in England are essentially similar to those in Victoria, but I would stress again the fact that in other places and at other times extensive immunization has taken place without any sequelæ of this kind. The possibility of a mutation of poliomyelitis virus having occurred must be kept in mind, but I do not think it is the only, or even the most likely, explanation of the phenomena. On the whole I am hopeful that the study of these occurrences will lead to fresh knowledge which will allow us to avoid them in the future. It is even possible that in the process we may obtain vital information on the most important clinical and epidemiological problem that poliomyelitis presents, what it is that determines whether an infection with the virus gives rise to paralytic disease, to non-paralytic symptoms or to a silent, wholly subclinical infection.

Section of the History of Medicine

President—E. Ashworth Underwood, M.A., M.D., D.P.H.

[*April* 5, 1950]

René Descartes, 1596—1650
A Short Note on His Part in the History of Medicine

By H. P. Bayon, M.D.

It can be ascertained that, in 1628, Descartes became particularly interested in attempting to solve by mathematical methods the problems of biology and medicine and to confirm the answer by anatomical observations and experimental methods; this study he continued till his death in 1650. That he failed in his task is due to the scanty fundamental information and data available at the time; those who followed him, like Borelli and also Baglivi, were unable to perpetuate iatro-physics, because medicine, as it was then understood, did not lend itself to mathematical investigation. It was only later, as in the last century, when instrumentation, together with biological knowledge, became an integral part of medical practice, that suitable observations were subject to mathematical proof. Thus the role played by Descartes in medical progress was more symptomatic than significant.

It might be said, with more assertive brevity than factual accuracy, that as Galileo was the father of modern astronomy, so Bacon inspired science, Harvey heralded the advent of contemporary medicine, and Descartes made the new philosophy. Such a list could be extended, but reflection will suggest that these names simply represent phases in a continuous process and that, however great the contribution to general progress of these eminent scientists, they had to rely on the knowledge of their predecessors. Admittedly, Descartes intended to make a clean sweep of all preconceived ideas—but did he, in reality? Even when adopting the opinions of Harvey in relation to the circulation of the blood, was not the French thinker fettered by the views of Galen in connexion with the action of the heart?

The tercentenary of his death is an occasion for explaining how it came about that Descartes, who was an eminent philosopher and clever mathematician, notwithstanding many efforts, did not succeed in making a single lasting discovery in medicine; nor did he recognize at their full value those that were being made in his time. A simple and homely comparison may help to explain. In geometry a straight line is the shortest between any two points—but the same axiom does not apply in all biological problems, for their solution is often obtained by the indirect approach. For example, the microscopical classification of Foraminifera, which provided most valuable indications in relation to oil-borings, or perhaps, better still, the experiments of Francesco Redi (1626–98) on the "spontaneous" generation of flies, which resulted in advancing the knowledge of bacteriology.

Such considerations may be kept in mind, when recalling the tercentenary of the death, on February 11, 1650, of René Descartes, even if opinions differ as to his significance in furthering medical progress. Thus Singer (1928) writes, p. 127: "A strong point in his theory is the great stress laid upon the nervous system and its power of co-ordinating the different bodily activities. Thus stated, his view is not far from the modern standpoint, though in fact he was grotesquely wrong in detail." In the *Bibliotheca Osleriana* (1929) Osler wrote, p. 76: "He (Descartes) was the first foreigner of distinction (though really, at the time, he was not known as an author) to accept Harvey's views." It can be recalled that Descartes also wrote on embryogeny and Needham (1934), p. 135, after quoting R. Garden (1693) as having said that in applying the laws of motion to the forming of an animal "how wretchedly Descartes came off", goes on: "In doing so he was many years before his time." Guthrie (1945), p. 176: "The effect of 'Cartesian' philosophy on medical science was considerable." In Castiglioni (1947) the subject is discussed at length and on p. 507 it is stated: "There is an essential connexion between the philosophy of Bruno (Giordano Bruno 1548–1600) and that of René Descartes (Cartesius), whose name has great importance for the history of medicine, not only on account of his personal contributions as physiologist and pathologist but also on account of the effect that Cartesian philosophy exerted on the evolution of medicine."

On the other hand, Creutz-Steudel (1948) do not mention Descartes or Borelli and only refer to Giorgio Baglivi (1668–1707)—the last of the iatro-physicists—in an indirect manner.

Lastly, Jefferson (1949) writes, p. 692: "It is evident from Descartes' letters, as well as from his writings, that he was deeply intrigued by medicine."

To obtain some clarity from these discordant opinions it is necessary to refer briefly to some details of the life of Descartes, hitherto overlooked and essential to any consideration of his relationship to medicine.

It is from 1626—the year of Francis Bacon's death, the news of which greatly affected Descartes—that the significant incidents can be observed. He had returned to Paris that year and there met the friend of his childhood days Marin Mersenne (1588–1648) and Claude Mydorge (1585–1647), a skilled mathematician—who revived the interest which Descartes had shown in geometry both as a schoolboy and young officer in the army—for up till then there was no hint that he intended applying mathematics to any but commonly accepted uses.

In 1628 an incident occurred which altered the outlook of Descartes, and was profoundly significant for his future activities. The Papal Nuncio, Cardinal de Bagni, held an assembly to hear a most eloquent Dr. Chandoux (who in 1631 died on the scaffold as a false coiner) propound a new system of philosophy; Descartes attended with Mersenne and Dr. de Ville Bresseux of Grénoble. Having been pressed by Cardinal Pierre de Bérulle (1575–1629) to take part in the discussion, Descartes showed that by arguments it was possible to prove the true to be false and the false to be true. Asked how these evils of sophistry could be avoided he answered that there was no truth that could not be demonstrated by mathematics. A few days later, Descartes visited Cardinal de Bérulle and explained how mathematical proof could be applied not only to mechanics, but also to medicine. The Cardinal thereupon impressed Descartes with the seriousness and importance of such a task—remarks which made a deep impression on the young philosopher; indeed, such was the effect on the mind of Descartes, that in March 1629 he departed for Amsterdam, for he held that only in Holland could he meditate in freedom and quiet. It is recorded that he was entered as a student in the newly formed University at Franeker on April 16, 1629, as: *Renatus Descartes, Gallus philosophus*. He returned to Amsterdam, where chemistry and anatomy occupied his attention. Baillet (1691), Vol. I, p. 196, mentioned that in Amsterdam Descartes visited the butchers' shops daily, taking home specimens for more careful dissection. It seems therefore all the more remarkable that he did not notice that nerves were solid and not tubes carrying the nervous fluid. Descartes then matriculated in the University of Leyden on June 27, 1630.

In 1640–42 Descartes made the acquaintance of Elisabeth, Princess Palatine (1618–80)—the daughter of the "Queen of Hearts"—with whom he corresponded in truly courtly style. In 1647 he began an exchange of letters with Christine of Sweden (1626–89) to whom he addressed a dissertation, discussing which could be more harmful, unreasonable love or unjustified hatred. The Queen summoned Descartes to Stockholm; he arrived in Sweden early in October 1649. He was soon received in audience by the Queen and Descartes, who since his youth had kept in bed till midday, had to become an early riser. The cold climate did not suit him, an old lung ailment (tuberculosis ?) flared up again and on February 11, 1650, after a short illness, Descartes died of inflammation of the lungs.

Such is a note of the relevant part of the life of Descartes; for our purpose the essential feature is that in 1628—in Paris—he became persuaded that the problems of biology and medicine were susceptible of mathematical proof. Once this start had been made, there is frequent proof of his keen interest in medical matters. In January 1630 he wrote to Mersenne —who was suffering from erysipelas—that he should preserve his health till he—Descartes—had discovered a system of medicine capable of irrefutable demonstration. Even so, he also wrote to Mersenne (Baillet, Vol. I, p. 197) that after eleven years of study there was no portion of the body he could not explain, but as yet he could not cure even a fever—an ailment he considered peculiar to man.

In the *Méthode* (1637), p. 62, he wrote: "There were endless possibilities before men of freeing themselves from maladies of body and mind, as well as from the debility of old age." Numerous other quotations could be made from the writings of Descartes to show his eager desire to apply geometry to the solution of medical problems; one instance among many is the posthumously published: L'homme et un traité de la formation du fœtus du mesme autheur (Paris, 1664). Of this work, Needham (1934), p. 135, says: "Descartes, in fact, with premature simplification, was trying to erect an embryology *more geometrico demonstrata*."

That Descartes promptly accepted the Harveian circulation of the blood can be mentioned, but what is particularly remarkable is that he did so in saying that Harvey had shown a communication between the arteries and veins by means of little tubes. This unfortunately was not a correct quotation, for Harvey not only had not seen the capillary connexion between arteries and veins, but did not believe it existed. Instead he thought that the blood oozing out of the finest arterioles was sucked up again by the endings of the veins—one

can assume somewhat in the manner a rivulet ends in sand and then re-forms itself lower down. In relation to the action of the heart Harvey and Descartes did not agree—for the latter said that when the heart contracted, it was preparing to expand and suck up the blood—according to Galenical doctrine.

Adrien Baillet—the biographer of Descartes, Vol. II, p. 543, discussed whether he discovered the circulation of the blood and concluded that he could have, had he not been forestalled by Harvey!

It is unfortunate that Descartes is more often remembered for the mistaken opinions he expressed than for the useful principles he propounded—for example that the pineal gland contained the soul of man—leaving out of consideration that animals, which had no soul, also possessed a pineal gland. To solve the difficulties of medicine by accurate methods was not a preposterous suggestion—it was only premature, for the necessary factual information was lacking. It was Giovanni Alfonso Borelli (1608–71) who made the only possible adaptation at the time—viz. the mechanical explanation of certain muscular movements, so that even to-day the same principles find application. It is with reason that Singer (1928), p. 129, can write that the achievement of Borelli was more lasting than that of Descartes.

Before concluding it may be mentioned that it has been often suggested that Descartes was influenced by the writings of Francis Bacon (1561–1626) who was greatly admired by the French philosopher. Reference is usually made to both when it is a question of describing the progress of the experimental method. There is, however, an essential difference between the aim of Bacon and of Descartes in the use of experiment; Bacon considered it a means of obtaining information about new laws and providing arguments for the discovery of new technical achievements. Descartes instead viewed experiments as the means for confirming doctrines due to mathematical reasoning. It can be assumed that he was impressed by Harvey's calculation of the output of the heart.

Therefore, though it is a misuse of words to say that Descartes contributed personally to physiological or even to pathological knowledge, yet it can be reasonably suggested that, by his advocacy of experiment as a confirmation of theory, by his attempt to make biological laws and medical observations amenable to mathematical proof (one cannot help recalling the doctrines of Alkindi (*c.* 873) of Bagdad in relation to posology), by his inspiration of iatro-physics—possibly a sterile, but not a retrograde system of medicine and, by no means least, by his efforts to combine physiology with psychology in relation to reflexes—Descartes deserves to be honourably remembered in the history of medicine.

Apart from the books mentioned in the text, great help has been obtained from: Elizabeth S. Haldane—*Descartes—His Life and Times* (London, 1905), Murray. A work I would gladly have read, but could not obtain, is: B. de Saint Germain—*Descartes considéré comme Physiologiste et comme Médecin* (Paris, 1870).

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The History of Diverticulitis of the Intestine

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IN what may be termed the natural history period of medicine there are descriptions of abnormalities of the intestinal tract varying from monstrosities to those compatible with life. These were summarized by Voigtel as late as 1804 and Fleischmann in 1815 without a very clear differentiation. The eighteenth century appears to have been an *epoch of doubt*, doubt about the significance of these anomalies and doubt about their causation. Leaving aside the monstrosities, the other forms were usually held to be the result of traction, especially in association with the entrance of portions of the intestine into hernial sacs. Littré (1700) believed that a diverticulum may be formed when part only of the wall of the intestine enters the hernial sac and not the whole diameter, so that only one side of the intestine is pulled out and finally becomes a longer and longer canal. Morgagni (1761), in discussing hernia, accepts this explanation in general for those diverticula, later to be differentiated by

Meckel, but goes on to discuss other than Meckel's diverticulum ilei which are also called diverticula and which can enter the hernial sacculus. Indeed, they could not all be preternatural and formed from the side of the intestine being prolapsed into the hernial sacculus, "for sometimes they belong to those intestines which are not situated in places where hernias happen".

Morgagni recognized the commonest one in the lower part of the ileum. He even had considered the hypothesis that this diverticulum ilei could be the remains of that duct which had formerly belonged to the vitellum. He had observed such a diverticulum in geese as well as in human bodies. Morgagni then goes on to quote the view of Fabricius that the reason these appendages happen in the ileum is that by absorption of the chyle the bowel contents as they proceed further in the intestine become dryer and harder, and therefore can exert pressure from the inside, instead of the traction from without.

Meckel (1812) clearly described the blind protrusion of the ileum as a process or diverticulum, occurring only in this part of the intestine; a congenital formation, consisting of all the coats of the intestinal canal and it may contain Peyer's glands. He showed that it is congenitally formed in relation to the umbilical vitelline duct or blood vessel and is found in animals, birds and reptiles. The earliest illustration is in Monro's pathological anatomy published in Edinburgh in 1811, which shows a portion of small intestine strangulated by a Meckel diverticulum.

Meckel, too, described another group where diverticula open inwards on the side opposite to the usual one, and are found burrowing in the mesenteric side of the intestinal canal after removal of the mesentery. Already in 1804 Sir Astley Cooper had illustrated such a condition in his book on the Anatomy and Surgical Treatment of Inguinal and Congenital Hernias. Astley Cooper and Monro were friends; Cooper spent some time in Edinburgh and Monro mentions both the non-Meckelian and Meckelian diverticula.

Before passing from the epoch of doubt as it moved to the *epoch of description* in the late eighteenth and early nineteenth centuries, I should like to call attention to a vein of knowledge which occurs throughout the literature of the succeeding time—what one might call the "near misses". Authors describe a condition, usually in the large intestine, in which the course of cases of diverticulitis is clearly given, but the significance of the inflammation of the diverticula is not mentioned or not stressed. I shall mention several instances of this as we proceed, the earliest being by Maximilian Stoll: *de Rationis Medendi* (1787). But in the book on Chronic Diseases by Stoll, published in 1789 a couple of years after his death and edited by his pupil Eyerell, there is a description which shows that he had observed cases of diverticulitis of the colon. This extract is from a chapter on Colica Stercorea.

"In this place also certain other not uncommon forms of Colica Stercorea may be recalled, in women who have had frequent pregnancies or are mothers of numerous progeny; the intestines have often a number of unequal sizes, being in places much dilated and in other places strongly contracted, so that fæces become greatly collected in the sac or diverticulum of the intestine and bowel action is delayed, the hard fæces irritate the intestines and cause colicky pain. This occurs most in the colon, especially at the flexures, either at the hepatic or splenic flexure or one of them. These diverticula, these enlargements of the intestines filled with hard and bulky fæces, may often be palpated and give the impression of sausages felt through the abdomen, and unless carefully observed are thought to be cancer of the intestine. This is not so, however, for within a few days when the bowels are well opened they may disappear or greatly diminish in size, though they may form again within a few days."

The next phase in the history of diverticulitis is what may be described as the *epoch of definition.*

Morbid anatomists gave clear descriptions of the pathological appearances at post-mortem examination (Cruveilhier, 1834; Rokitansky, 1842; Jones and Sieveking, 1854; Bristowe, 1855) and Sidney Jones (1858) described the first case of vesico-colic fistula due to diverticulitis of the sigmoid.

Meantime the clinical importance of these cases was becoming recognized in the colon (Habershon, 1857; Hale White, 1885) and in the jejunum (Osler, 1881).

In this phase of definition the incidence of acquired diverticula of the intestine is established, and discussion centres round the ætiology of the diverticula and their consequences to the patient.

Klebs in 1869 suggested a causation other than pressure of intestinal gases or fæcal masses. He pointed to the relation of the site of the diverticula in the small intestine near the mesenteric border at the places of penetration of the blood-vessels and debated whether the pull of the vessels which do not stretch with the lengthening of the mesentery contributes both in early development and in the visceroptosis of late adult life. Klebs found the smallest diverticula had no true muscular coat and were herniæ of the mucous membrane layer.

Edel (1894) illustrates the post-mortem appearances of the intestine from inside and outside, and in a dissected specimen shows the intimate association of blood vessels and the diverticulum. He gives an early picture of a diverticulum of the appendix.

Hansemann (1896) found in experiments on animals that raising the intestinal pressure in the intestine caused rupture before there was evidence of sacculation. He found, however, he could blow out these small herniæ in adults and still more easily in the bowel of elderly patients, though he could not produce them in children. He postulates a lowered resistance of the bowel wall with ageing. Beer (1904) was also of the opinion that weakness of the muscle was the cause of the formation of these diverticula.

A third factor is a change bringing about a lowered resistance in the wall, particularly the muscular coat, of the intestine, thus allowing herniation to occur more readily. Various suggestions have been made for the cause of such changes. Deposits of fat on the course of the vessels, subsequent atrophy of these fat deposits from wasting, the presence of rests of pancreatic tissue in association with ducts and blood vessels, especially in the case of the duodenum and upper jejunum, and congestion of the intestinal veins in heart disease have all been offered. There may be localized changes in resistance of the wall resulting in muscular deficiency. Small foci of infection from bacteria passing into the submucosa and producing a leucocytic accumulation which, after absorption, leaves a fibrous dilatable scar were mentioned by Wilson (1911). Local spasm of the muscular coat causing herniation is emphasized by Edwards (1936) on the grounds of the relation of the pouches to the circular muscle; Barling (1926) saw an example of such spasm in a colon exposed at operation. It may well be that degeneration and atrophy of the muscular coat occur with ageing, and that it is a phenomenon of wear and use, combined with changes in the vitamin supply and biochemical reactions from waste products and deficient oxygenation. The pathogenesis of diverticulosis in the small intestine has not been much advanced since Fischer in 1899 made the best contribution up to that time on the appearances, both in the dead body, on dissection and on microscopic examination.

A full discussion of the knowledge thus obtained and a summary of 105 cases collected from the literature by Maxwell Telling (1908) forms the best résumé of the subject in its clinical and pathological aspects before radiology brought in the *epoch of demonstration.*

Meantime, with the beginning of the heroic age of abdominal surgery, cases of diverticulosis of the colon were coming to operation. In 1896 William Mayo operated on his first case of internal fæcal fistula into the bladder, and later had resected the colon in cases thought to be cancer which were found to be diverticulitis. Bland-Sutton in 1903 removed a portion of colon thought to be cancerous. There was found to be a foreign body (straw) in a fæcal mass in diverticulitis of sigmoid. Moynihan in 1906 reported a series of such cases in which diverticulitis simulated cancer and on successful resection were found to be due to diverticulitis. At a full-dress debate on the subject of diverticulitis of the colon at the subsection of Proctology in 1920, other cases were mentioned (Morrison, 1903). But these cases were surprises rather than diagnoses, and in the discussion several surgeons expressed the view that diverticulitis might have been the underlying factor in some of the cases which had puzzled them. This is the more astonishing as already the development of X-ray technique had enabled the diverticula to be demonstrated and a diagnosis to be made.

Case in 1913 had shown X-ray plates of duodenal diverticula to an American Roentgenological Society. His paper was published in 1916 and is a classical demonstration of the condition. However, in a later paper (1920) he gives precedence to Forsell who in 1915 published the first case of a duodenal diverticulum diagnosed by X-ray and confirmed at operation.

There is some doubt about the priority of X-ray diagnosis of diverticulitis of the colon confirmed at operation. I think the earliest was published in 1914 by de Quervain.

Carman in 1914 at the Mayo Clinic produced pictures which enabled William Mayo to diagnose diverticulitis and deal with it surgically. But Carman gives precedence to Abbé who, with Lewald (1914), demonstrated diverticulitis of the colon and successfully removed the affected portion of the bowel.

I have mentioned the many instances in which the finding of diverticula has come as a surprise and I have already referred to the fact that in the literature of the last two centuries there are descriptions of cases in which the probable cause originated in diverticula and their complications, where the symptoms were attributed to various causes from constipation to cancer.

Stoll (1787) describes tumours in the hypochondriac regions in people with sedentary occupations, such as writers and others, due to distension of the flexures of the colon which are not to be confused with tumours of the spleen and liver.

He had formerly observed these painful tumours in the epigastrium or hypochondria of women after childbirth, more or less movable in different positions of the body. He believed them to arise in portions of the intestine distended into sacculi, or where the intestinal wall is dilated, perhaps from the pressure of the gravid uterus. He cured them with soapy enemata.

Virchow in 1853 quotes Stoll and goes on to explain the hypochondriasis, with irregularity of the bowels, digestive disturbances, and troublesome sensations in the lower abdomen. "In these cases there is often a chronic partial peritonitis, especially at the sigmoid where there may be a piling-up and retention of fæcal masses."

John Bright in his *Clinical Memoirs of Abdominal Tumours* (1860) describes cases of fæculent tumours of the large intestine which might be confused with tumours of the liver.

Humphry Rolleston in 1905 in an article on *Pericolitis sinistra* describes three forms of the condition: (1) acute circumscribed local perisigmoiditis; (2) local abscess with perforation of a stercoral ulcer; a fistula had formed in one case from a false diverticulum of the colon into the bladder; (3) rupture with peritonitis.

Rolleston gives cases illustrating these forms and quotes Beer who had called attention to four cases of false diverticula perforating into the general peritoneal cavity.

Rolleston apparently did not give the significance to the wall of the diverticula as the focal point of infection and the source of the inflammation which is accepted as the pathological basis of the symptoms at the present day.

Now having traced the history of diverticulitis of the intestine from the epoch of doubt, through its description, definition and demonstration, I think the condition is one which should occur to the clinical mind in the differential diagnosis of abdominal symptoms.

Addendum—Nomenclature

A diverticulum is a smaller side-branch of any cavity or passage; in anatomy it is applied usually to a blind tubular process, in pathology to a malformation having this character. Diverticula or accessory pouches of the intestine—as distinct from monstrosities—were noted in the "natural history" period of medicine and were regarded as sometimes natural as the appendix vermiformis, or at other times as developmental anomalies. In the intestinal tract these preternatural diverticula were described as the result of false joining-up of the fore-gut and after-gut. The name was carried over to other protrusions of the wall of the intestine and Morgagni uses sacculi as synonymous with diverticula. Inflammation of the tissues of the gastro-intestinal wall surrounding the diverticula led to the adoption of the generic term diverticulitis; but de Quervain (1914) introduced the term diverticulosis to distinguish simple sac formation from the advanced stage with local inflammation called diverticulitis. For a time the cavity of a penetrating ulcer of the duodenum or stomach was called ulcer-diverticulum by American authors (Case, 1916) but this term has rightly lapsed into desuetude. Spriggs (1929) suggested the simpler term sac with its derivatives saccosis and saccitis for the sake of brevity—Maximilian Stoll (1789) uses saccus as an alternative to diverticulum in his discussion of forms of colica stercorea; but "diverticulosis" and "diverticulitis" now appear to be firmly established in medical literature. In 1923 Marxer drew attention to the X-ray appearances in the earliest stage before herniation of the mucous coat is established and has described this as the "pre-diverticular state". We have followed patients over many years in which such appearances are found to go on to established diverticulitis.

A Swiss colleague informs me that diverticulitis of the colon, especially the sigmoid portion, is known in Switzerland as *Mayor's disease*. A. Mayor (1907) published descriptions of the history, course and treatment of sigmoiditis and perisigmoiditis, mentioning the presence of acquired diverticula in the pathogenesis (p. 598).

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Fifty Years of Physiology

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GENERAL INTRODUCTION

THE efficient cause of this review is the importunity[1] of my friend, Dr. E. Ashworth Underwood; the final cause is my regret that the *British Medical Journal*, in its otherwise very laudable survey of progress in medicine from 1900 to date (*see* Various authors, 1950), failed to include any mention of what were once styled the "Institutes" of that subject. Speaking in 1937, Carlson stated that "Physiology is to-day even more important in the medical school, in the training of physicians, than it was fifty years ago, and I see no indication of its diminishing importance in this field" (*see* Various authors, 1938, 219). With thirteen more years than he had to look back upon, we can say with assurance that the *major* advances in medicine are coming more and more from the laboratory side, represented by functional zoology, functional anatomy, biochemistry, pharmacology, study of antibiotics, experimental pathology and medicine and the like in addition to physiology itself. All these others have adopted research procedures very akin in principle, and to some extent in technique, to those of physiology itself, and the dividing lines between the various disciplines are often difficult to discern even if, for convenience of administration and so forth, the departments retain their individual names.

The strategy of modern medicine is, then, tending ever more and more to derive from the laboratory while the tactics remain the sphere of the wards. Many clinicians have realized this tendency and are preserving their share in the strategic direction by the valuable contributions which they are making, by extra determinations on patients (e.g. through catheterization studies of the blood in various parts of the cardiovascular system), to knowledge of human physiology and of the departures from it caused by disease; others carry out experimental work, in its usually accepted sense, in addition to their attendance on their patients. This healthy and welcome trend on the clinicians' part towards integration of the two sides is aided by the increasing tendency for the laboratory workers to visit the wards and thereby to gain a better appreciation of the problems presented by the disordered physiology of man.

This has not yet led to any much greater proportion of practical physiology class-work being carried out with man himself, rather than lower animals, as the subject. Nor, I think, is it very likely so to do. For Fulton's (1930) analysis shows that man has always in large measure been his own guinea-pig in research, and human respiratory and metabolic and other studies have long formed a considerable part of practical courses in medical schools; finally, demonstrations of some facts of importance preclude, or militate against, survival of the subjects, so there must always be some animal "experimental physiology" for students. On the research, as opposed to the teaching, side I think there is absolutely, though probably

[1] "Troublesome pertinacity in solicitation."—*O.E.D.*

not proportionately, more work being done now on the human subject. The *absolute* increase is due to stimuli coming in large measure from the clinical side. The lack of any great *proportionate* rise is due to the fact that physiology is not only an institute of medicine, but also a science in its own right, so that many of its practitioners, especially with modern increase in specialization, are neither medically qualified nor principally interested in the applicability of their findings to the understanding of the diseased human being. We should not, as medical men, discourage these others, for the histories of all sciences contain many examples of what began as "pure" and ended, often unexpectedly and sometimes very advantageously, as "applied".

After the above remarks I am faced with the problem of how best to deal with the rest of my subject, a survey of a vast field over a period arbitrarily selected and with no outstanding event marking either its beginning or its end.[2] The person who could produce the ideal review is Sir Charles Sherrington, now in his ninety-third year but with his wide and retentive memory unaffected by the attainment of what I believe is a record age for any physiologist in the whole, long history of our science. Fifteen years ago, with considerable reluctance because he disliked being in any way autobiographical, he gave in Oxford a talk on "Nineteenth *fin de siècle*", and I have refreshed my memory of it by re-reading the notes which I then made. They do not, however, carry on to this century and I can only say that they give a valuable impression of physiology at a younger and more intimate stage when Michael Foster ("an influence rather than a discoverer, a discoverer of people rather than of facts") was one of the dominant personalities in the science, not only in Cambridge and in Great Britain generally, but also internationally. Through later recollections furnished by Sir Charles Sherrington, and further ones from J. S. Haldane, Sir Joseph Barcroft, and others and from the literature, I have to build up my ideas of the first two decades of this century; in respect of the next three, I have in addition some of my own memories to assist me.

Some idea of the growth of physiology is acquired from details of the increase in number of those professionally interested in the subject, and Fig. 1 demonstrates this increase in

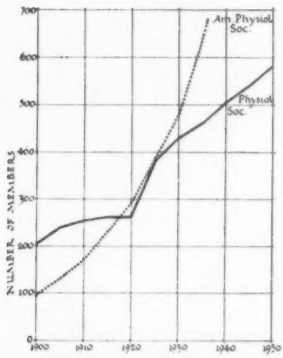


FIG. 1.—Graph showing increase in membership of the Physiological Society (details kindly furnished by Professor D. Whitteridge, Hon. Secretary) and of the American Physiological Society (*see* Various authors, 1938, 176–7).

respect of membership of the Physiological Society and of the American Physiological Society respectively. It is shown even more markedly in the attendances at the triennial International Congresses (Fulton, 1931, 109). With regard to the Physiological Society, the graph would show a sharper upward trend but for the necessity, increasingly felt in recent years, for restricting the membership. It is of passing interest that the first woman member of the American Society was admitted in 1902, while the Physiological Society remained exclusively male until 1915. The Canadian Physiological Society was founded in 1935.

Increase in personnel has been accompanied by many other changes, e.g. advances in technique, reorientation of outlook, increase in specialization, splitting off of biochemistry and to some extent of biophysics, multiplication of journals of interest to physiologists, and the like. Some of these I have already mentioned in a prospective publication (Franklin, 1951) so I will confine myself here mainly to the increase in specialization and to the reorientation of outlook. The former is linked up with advances in technique (which allow

[2] An event of some *interest*, on the other hand, marked its beginning. This was the delivery by Michael Foster in 1900 of the Lane Lectures on the history of physiology during the sixteenth, seventeenth and eighteenth centuries.

infinitely more rapid performance of those things which could be done in 1900 and potentiate researches not then possible), with the vast increase in the literature, and with the developments occurring in the physical sciences. Fifty years ago the physiologist could also be, and often was, a physiological chemist and a histologist; he could also claim to be adequately versed in the whole of the literature of his subject. Now, almost without exception, the physiologist, biochemist, and histologist are separate persons, and to know even a small section of the literature well is the most that any one person can claim. With the increase in specialization there has also been (*see* Fulton, 1931) a sharper cleavage between those physiologists who are mainly biological in background and those whose chief allegiance is to the physical sciences.[3] We need both types, but the heterogeneity is not without its drawbacks and it is imperative that we have among our number some who are able and prepared, from time to time, to integrate the diverse contributions. Otherwise, the divided efforts, excellent in themselves, must be largely nugatory in respect of the science as a whole.

More interesting is another feature which I mentioned above, namely, a reorientation in outlook. The implications of Claude Bernard's idea of the constancy of the "milieu intérieur" were not immediately appreciated; indeed, the concept itself was little mentioned before 1920. Whether it focused attention on the individual cell and its importance in physiology, or whether the increasing attraction exerted by the cell on biochemists and physiologists at last produced the right conditions for the burgeoning of the seed planted by Bernard, is hard to decide. At all events, the large measure of diversion of interest to the individual cell is the major reorientation of outlook which has occurred in physiology between 1900 and 1950 and once again, provided there is adequate integration of the findings so that we acquire a picture of the body functioning as a whole, every encouragement can be given to the difficult attacks upon the problems posed by the cell, and every congratulation to those who, despite the difficulties, are unravelling its mysteries. For the later evolution of Bernard's concept, reference can be made to Cannon (1929), Barcroft (1934), and Olmsted (1939).

So much for *some* of the general points, and I must say that I have by no means exhausted the list. I will pass now to a brief consideration of the advances in four of the individual sections of physiology. My account of these four is derived from various sources, including the story of the International Congresses (Franklin, 1938); one of the objects of those meetings is to provide triennially a survey and demonstrations of new discoveries, and we can see in contemporary accounts of them which items were at the time most impressive. This is of importance, for a new finding is little more than a curiosity of history unless it is accepted and incorporated into the general fabric of knowledge. Apart from this and other means, I have compared Starling's *Elements of Human Physiology* (1900)[4] with its lineal descendant, Lovatt Evans' *Principles of Human Physiology* (1949), and with other textbooks. With regard to what, in more recent years, should be regarded as biochemical rather than physiological, I have had no very precise rule, for biochemistry separated at different times in different universities; the Continent preceded Great Britain, and in Great Britain the initial sequence was Liverpool (research only) 1902, Cambridge 1914, and Oxford 1922. As the period from the foundation of the Oxford Chair onwards is within my personal recollection, I am going by my impressions of what physiologists claimed as pertaining to their science or regarded at least as still an essential part of their subject. This is justifiable, for it was really only increase in size and so forth of the parent science which caused it to undergo mitotic division!

Fœtal and Neonatal Physiology and Normal Gerontology

The physiological range is from conception to death, but until the middle of the period we are reviewing there was very little precise knowledge about intra-uterine functioning, while the inquiry into what is normal at the other end of life was only seriously inaugurated even more recently.

For the more definite information which we now have about the former, as also for the stimulus to explore farther this interesting and fruitful field, we are indebted *imprimis* to the late Sir Joseph Barcroft, and it is a matter of real regret that his sudden death in 1947 prevented him from following up his *Researches on Pre-natal Life* (1946) with the envisaged second volume.[5] Such work is important not only because it fills out the first part of the mammalian physiological story, but also because the functional apparatūs come into service *seriatim* during intra-uterine life, so that it is possible, for instance, to separate the earlier,

[3] I can remember being somewhat shocked, a generation ago, when a newly appointed Professor, in his inaugural lecture, said quite frankly, "I am a physicist, not a physiologist".

[4] There were also 1900 editions, in two volumes each, of Howell's textbook and of the more monumental one edited by Schäfer.

[5] The first line of the Preface of Volume I read: "This work partakes much of the nature of a will—I hope not my last."

direct actions of carbon dioxide excess and oxygen lack from those which they exhibit after the parts have become innervated, or the functions of the first-developed cerebrospinal centres from those of the later-perfected ones. In other words, at stages in pre-natal life there is a natural absence of complicating factors which can only be paralleled post-natally through experimental procedures. Much has already been learned, but much more remains to be learned, by the seizing of such opportunities.

Neonatal[6] physiology (*see*, e.g., Clement Smith, 1946) also has attracted considerable interest and been the subject of much research in more recent years, though a vast amount remains to be done. Nor is the functional picture by any means complete during the rest of the pre-adult stages.

The physiology of old age is even less well understood, and there is need for the establishment of standards by which the departures from normal, which are at present the lot of most elderly people, can be determined. With the increasing attention now being paid to the problems of old age, these standards will come, one imagines, before very long and they will be a stimulus to the attainment of the major objective proclaimed by the *Journal of Gerontology*, namely: "To add life to years, not merely years to life."

Endocrine Glands

The term "internal secretion", defined as a secretion the product of which is passed directly into the blood instead of to the outside of the organ, was coined in 1855 by Claude Bernard and was first applied to the glycogen production of the liver, though this is now no longer regarded as an endocrine activity; later he included the thyroid and adrenals in his list of glands of internal secretion. However, with the exceptions of Oliver and Schäfer's paper (1894) on the pressor effect of adrenal extract and those of the same workers (1894–95) and of Howell (1898) on the pituitary, the rest of the nineteenth century part of the story consists, in the main, of useful pointers from the clinical field (*see* Rolleston, 1936, for details). For such suggestions, however, physiologists as a whole were not yet ready, and Starling (1900), in his chapter on the ductless glands, wrote as follows: "Under this title have been grouped a number of organs, the sole resemblance between which lies in the fact that we know very little about them. Since, however, they seem to exert important though obscure influences on the nutrition of the body, they may be fitly discussed at the end of the chapter on metabolism. In many instances their functions seem to be to furnish an 'internal secretion' to the lymph or blood which leaves them. This is almost certainly the case with the thyroid gland, but the exact nature of the secretion or its action is in all cases very difficult to determine. . . . The chief ductless glands are the spleen, thyroid, thymus, and suprarenal capsules, but besides these, other glands such as the pancreas, ovaries, testes have been thought to influence the body by means of internal secretions. We have also to mention the small bodies of unknown function such as the pituitary body, the pineal body, the parathyroids, the carotid and coccygeal glands."

We can, therefore, state that almost all the vast and important knowledge that we now have of the endocrine glands and their products has been accumulated during the last fifty years. Perhaps the outstanding single item is the contribution of Banting and Best, announced to the American Physiological Society at its meeting in New Haven in December 1921.[7] But there are numerous others and the full list is a truly wonderful record of accomplishment. Fortunately, in so far as my time this evening is concerned, adequate historical notes are now inserted in the larger textbooks of physiology and I can pardonably restrain my inclination to detail the names and achievements of the other contributors to progress in this section of our science.

The Circulation

Many technical advances have aided research on the blood circulation. They include electrocardiography, effectively introduced by Einthoven[8] just after the beginning of the century; the use of Starling's heart-lung preparation in its various forms; optical recording methods, in the designing of which Wiggers was the pioneer in the twenties; Rein's Thermostromuhr of 1928; and direct and indirect cineradiography, combined with intravascular

[6] This hybrid word appears to have come to stay, and all that one can do is to register an ineffective regret that it was coined.

[7] An interesting feature of the insulin story is the early coining of the name (de Meyer, 1909; Sharpey-Schafer, 1916) for the as yet unisolated product of the islet cells. A most curious feature is the extraordinary behaviour of Gley (*see* Macleod, 1926, 68).

[8] Though A. D. Waller's work preceded his (*see* Waller, 1950).

injection of radiopaque substances, the effective use of which began soon after 1930. These last techniques, associated with the names of Janker, Barclay, and others, have the great advantage of showing up circulatory happenings within the *intact* body and they are applicable not only to animals but also to man, e.g. as diagnostic aids and guides to the surgeon in cases of congenital cardiac defects (Janker, 1950).

In the nineteenth century the heart and the arteries were the parts of the cardiovascular system which received most attention, over the turn of the century the arterioles were coming into the picture, during the 1914–18 war and immediately after it the capillaries followed suit, and a decade later the veins also began to be regarded as of interest. With the work of Barcroft and his colleagues from 1923 onwards, the volume of the blood circulating through the system was shown to be variable within wide limits, and the idea of blood-depôts or blood-stores entered into physiological concepts.

The functioning of individual sections of the system, and its nervous and chemical regulation, have received detailed attention in the chronological order: coronary circulation, pulmonary circulation, fœtal circulation, renal circulation, and hepatic circulation. In among these detailed studies, a few persons, e.g. Rein, have attempted to record simultaneously events in several different parts of the system, while the radiographic studies at the Nuffield Institute for Medical Research, Oxford, from 1945 to 1947 gave an even wider view without operative intervention. The fine programme[9], however, of which those studies were to have constituted merely a beginning, has been carried little farther, and in general we have few well-documented pictures of circulatory activity as it occurs simultaneously throughout any great portion of the total cardiovascular system. Even more important, there is no proper account of the integrative action of the blood-circulatory system to correspond with Sherrington's classic on the integrative action of the nervous one. Though, however, such criticisms of the present position are fully justified, one has only to read what was known in 1900 to appreciate the enormous advances, only some of which are mentioned above, which have come about since then.

Studies of the lymph flow bring to mind the names of Starling, Drinker, McMaster and many others. Technically, the lymphatic circulation is one of the most difficult of the body's processes to investigate, and the delicacy of the more recent work has invalidated certain of the conclusions arrived at by earlier workers with their more cumbrous techniques. There is not, however, full agreement at present among the leading authorities and in consequence I will not attempt any precise assessment of the present position; I will, instead, mention two out of many contributions of interest. The first is that of Barnes and Trueta (1941) on absorption of bacteria, toxins and snake venoms from the tissues; it showed, *inter alia*, that substances with molecular weights of over 20,000 were absorbed into lymphatics and not into the blood stream, and that immobilization prevented such lymphatic absorption. The second contribution was that of Crandall, Barker and Graham (1943), who studied a patient suffering from a thoracic duct fistula as a result of a gunshot wound, and found that the daily loss of protein was 92 grams per day and the weekly loss of body-weight over 2 kg. These and other twentieth-century studies are of great interest, but there have been notable contributions from the time of Lower (1669) onwards, and I should regard the developments of the last five decades as representing steady rather than spectacular progress.

The knowledge of the cerebrospinal fluid and of its circulation was greatly advanced by the studies of Lewis H. Weed and his colleagues during and after the 1914–18 war. Neurosurgeons have provided extra information as the result of observations made during brain operations, and the story is now in no small measure revealed; certainly, knowledge is very much greater than it was in 1900.

Having considered separately in the above ways the blood, lymph, and cerebrospinal fluid circulations, we have still to integrate all these and the movement of fluid within the tissue spaces and in and out of the tissue cells. Here, however, we must acknowledge our indebtedness to the biochemists, for it is their work with isotopes since 1923, carried on at an accelerated pace in recent years, which has revealed the immensity (7,000 litres per day)[10] of the fluid change-round which is continuously occurring. It is my view, which I hope to develop in a separate publication, that such findings demand an extension of the meaning of the word "circulation" to include all intra- and extra-vascular movement of water and solutes. Increase of knowledge is of importance in itself, but the linking up of various additions to knowledge in a new concept is real progress, and in this section of physiology we can claim to have achieved such with the help of our friends, the biochemists.

[9] "A full-scale experimental study of the effects of direct, central, and reflex stimulation of vascular nerves upon the various organs of the body" (Trueta, 1945).

[10] The phrase, *πάντα ῥεῖ οὐδὲν μένει*, is applicable to this huge fluid movement, in consequence of which the very tissue cells have similar, but not identical, components from minute to minute.

Respiration

In 1897 Mosso published his acapnia theory of mountain sickness, in 1899 Haldane produced his *Methods of air analysis*, the former destined to hold up acceptance of the right view for twenty years, the latter the prelude to a long series of important researches by its author and his various collaborators. With the new century, Barcroft's work soon began to be of importance; it was to result in 1914 in the first edition of his book, *The Respiratory Function of the Blood*. Among the ventures of the respiration experts the series of investigations of the effects of great altitudes and of underwater diving are notable. The former include the work on Monte Rosa (1911), Pike's Peak (1911), and the Andes (1921–22), and can be integrated with findings on Mount Everest (1924) and Mount Kamet (1931). In addition to their study in mountain ascents and diving, the respective pressure and related problems have been subjected, since the later stages of the 1914–18 war, to analysis in pressure chambers. With the increasing use of high-speed flying, problems of acceleration have been added to the pressure ones, and there is not space to detail here the enormous increase in knowledge resulting from the 1939–45 wartime researches on these matters in various countries. Study of diving problems has also continued on an increasing scale since Haldane's pioneer investigations, and I have personal recollections of a most interesting and instructive visit, a year or two ago, to the ship specially constructed for such work, H.M.S. *Reclaim*; I remember also illuminating demonstrations and film-projections given at meetings of the Physiological Society. The work on altitude effects which I have mentioned exploded Mosso's acapnia theory after its persistence through two decades; the work on altitude and diving re-established the correctness of the general principles enunciated in 1878 by Paul Bert, one of the greatest names associated with respiratory research.[11] A particular feature, little known in this country, of the action of altitude on respiration was described by Verzár and his colleagues (*see* Verzár, 1934).

Research on the nervous regulation of respiration was initiated by Le Gallois in 1811; in the present century there has been much work on the respiratory centres, beginning with that of Lumsden (1923) and continuing on to that of Magoun, Pitts, and Ranson (1939) and others in more recent times. Recording of action potentials has cleared up many points in respect of the activities of the peripheral nerves concerned, and in addition we have learned of the parts played by the carotid sinus and, more particularly, of the carotid body in respiratory control.

Thanks to the work of many people the uptake, carriage, and liberation of gases by the blood has been elucidated to a degree undreamed of thirty years ago. The method for the determination of the velocity of combination of oxygen and hæmoglobin (Hartridge and Roughton, 1927), demonstrated at a meeting of the Physiological Society, is one outstanding item remaining in my memory, but it is only one of many.

I will not make any long mention of the modern discoveries about tissue respiration, heralded by Hopkins' (1921) announcement of "an autoxidisable constituent of the cell", for these lie more within the province of the biochemist. Suffice it to say that together they form a magnificent thirty years' achievement.

I should however like, before closing this section, to refer to Barcroft and Barron's interesting work on the genesis of respiratory movements in the fœtus, and to the companion findings about the onset of pulmonary respiration at birth, for this rapid, and normally fully efficient, beginning of a novel activity is surely one of the most astonishing performances in the whole of mammalian physiology.

Nervous System

Before 1900, as can be gathered from accounts of the second, third and fourth International Congresses, the genius of Langley and of Sherrington was widely recognized. From then until his death in 1925 the former continued to add to precise knowledge of that part of the nervous system to which in 1900 he gave the name "autonomic". Sherrington, his erstwhile pupil, took the nervous system as a whole for his field and its major function, namely, its integrative action, as the main thesis to be developed. Fully to appreciate the measure of his achievement, we must realize the disconnectedness of the several contributions to knowledge which preceded his own.[12] His book, *The Integrative Action of the Nervous System*, which appeared

[11] J. S. Haldane once told me that Claude Bernard was his inspiration as regards thought, and Paul Bert as regards technique.

[12] A very full and well-documented account is to be found in the book written by Jules Soury (1899), which Sherrington himself read with considerable care but which is, unfortunately, extremely rare. I myself have seen but one copy of it and that was Sherrington's own one.

in 1906, remains *the* classic of neurophysiology and still needs to be read by anyone seeking understanding of that subject, even if the experimental work described in it was done by means of the old-fashioned myographs and smoked-surface drums. Sherrington continued to use these until about 1921, after which his optical myograph was brought into use and a further series of papers came from him and from his pupils on myotatic reflexes, recruitment, and so forth. This work was, in effect, a redirection of effort towards the understanding of the events at the synapse, and it has catalysed further studies not only in Great Britain, but in many other countries. The actual findings, however, are part of current teaching and need no detailed mention here.

Great also, if not *so* great and if great in a narrower field, was Rudolph Magnus, whose initial nervous system researches in Sherrington's laboratory in 1908 led on to the remarkable series of studies carried out in the Pharmacological Laboratory at Utrecht, and to the publication in 1924 of the second most stimulating neurophysiological book of our period, namely, *Körperstellung*, or body posture. An English résumé appeared in 1926 (Magnus, 1926), but in the next year Magnus' sudden death at Pontresina stopped further team work by the Utrecht school.

A third important book was the English edition (1927) of I. P. Pavlov's work on conditioned reflexes. As, however, most of the literature on that subject is still available only in Russian, I shall refrain from attempting to assess the whole.[13]

Many names are associated with work on the peripheral nerves, among the best known before 1921 being Keith Lucas and his pupil, Adrian. In 1920 Gasser and Newcomer began work with what was for our science a new instrument, namely, the cathode-ray oscillograph, and thereby opened a new chapter of neurophysiology. In the same year Otto Loewi inaugurated work on what became known as the humoral transmission of nervous impulses.[14] The subsequent story, with the coining of the words "adrenergic" and "cholinergic" by Dale and the other steps towards clarification and elucidation of the subject, is well known; it is a remarkable substantiation and extension of Elliott's ideas promulgated in the first decade of the century. Other remarkable achievements are Adrian's amplification and recording of nervous impulses, the success attained in the delicate localized stimulation of centres in the central nervous system, the discovery of the hypothalamus and of its multitudinous functions, increase in knowledge of the cerebral cortex and its connexions, and so forth. One venture which I would single out for special mention is Fulton's large-scale work on primates in New Haven. Much of the neurophysiology in the earlier part of the century was derived from experiments on species far removed from man. To Fulton, I think, more than to any other we owe the more relevant information now available.

Concluding Remarks

In preparation for the first edition (1933) of my history of physiology, and before I realized that I should have to stop short at the end of the nineteenth century, I made a list of important events and contributions associated with each year of the present century. Looking through that list, I am acutely conscious of how much I have perforce omitted from the review which I have given to-day. The rough and incomplete sketch, however, must for the time being serve in lieu of the finished picture, and I must leave those gifted with imagination to envisage what the whole might have been had the time at my disposal been longer and the space for publication greater. In many instances I have not referred, or have not referred at any length, to achievements of recognized importance; my excuse is that they are sufficiently well known without any mention of them by me, and that my hearers can readily integrate this other information with that which I have given. Here and there I have inserted items known to but few others, so that these items shall not pass into oblivion and be lost to history. Some matters I have not mentioned because I have already dealt with them elsewhere (Franklin, 1949, 1950, 1951), and in general I have tried to show trends rather than to stress mere increase in knowledge. Those who wish for a more precise estimate of the latter can quickly

[13] *See*, for an assessment by one of Pavlov's fellow-countrymen, Bykov (1950).

[14] The story, as told in Loewi's own words, is most thrilling: "Dans la nuit, mémorable pour moi, du samedi au dimanche de Pâques 1921, je me réveillai. Je tournai le bouton de la lampe, et j'écrivis quelques mots sur un petit morceau de papier mince. Puis je me rendormis. Vers six heures, la mémoire me revint que j'avais écrit quelque chose qui me paraissait important, mais je ne pouvais plus le déchiffrer. Je passai tout le dimanche dans un état de profonde dépression à tenter de déchiffrer ce que j'avais écrit, mais en vain. Mais la nuit suivante, je me réveillai à nouveau, et l'idée me revint. Il était trois heures du matin. Je me levai aussitôt, et je me rendis au laboratoire, j'isolai un coeur de grenouille avec ses nerfs, j'excitai le nerf vague et je transportai le contenu de ce coeur à un second coeur avec ce résultat que celui-ci cessa aussitôt de battre. Et, à cinq heures du matin, le mécanisme chimique de la transmission de l'excitation nerveuse était clairement démontré."

do as I myself did, namely, read a textbook of 1900 and compare it with one of to-day. It is worth while to do this in any case, for a contemporary account of the knowledge available fifty years ago has about it a "period" feeling which I cannot hope to recapture in words. May I, in conclusion, say that I include in the history of physiology that which is being discovered by researches to-day? I am not interested in the past merely as such, but rather in the continuity between all that was fine and great in that past and the original investigations which are even now proceeding.

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Section of Psychiatry

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DISCUSSION: PSYCHIATRY AND THE SKIN

Dr. R. M. B. MacKenna:

That skin eruption may be due to psychological causes is not a new conception: Charcot, for example, was not unaware of the relation of certain cutaneous lesions to hysteria, and Jonathan Hutchinson in 1876 observed that severe cheiropompholyx occurs usually in association with a highly nervous temperament ; he stated that the disease "must certainly be regarded as a neurosis". Examples from earlier authorities could be quoted, but these two must suffice. The matter which all must deplore is that many years elapsed between the original observations and the commencement of any thorough investigations concerning the relation between psychological disturbances and cutaneous eruptions or injuries.

At present there are two diametrically opposed beliefs concerning the relationship of the mind and the body in the ætiology of skin diseases. The first view is that if skin patients show psychological aber ations they do so beca se of their cutaneous diseases : the second that patients may produce various cutaneous abnormalities because of psychological disturbances. Doubtless many will dismiss the first hypothesis, but it contains a certain amount of truth: few persons can experience the misery, discomfort and unsightliness of some persistent skin disease without suffering some degree of psychological trauma, and thus secondary psychological effects may put difficulties in the way of the enquiring psychiatrist and must be "allowed for" by the dermatologist. For example, the patient with chronic rosacea may react adversely to the knowledge that friends and neighbours are hinting that he is a "chronic alcoholic", whilst the unsightliness of acne vulgaris—or of the scars left by the lesions—may greatly interfere with a girl's self-confidence and gravely affect her attitude to the social problems of her life so that she may become a recluse, or—thinking that acne is a visible sign of masculinity—may become as aggressive and as masculine as she can make herself, prolonging a state of unstable psychological equilibrium which may eventually lead to a breakdown.

Anxiety following a skin disease is a further example of a psychological disturbance. Adult males suffering from alopecia areata, particularly when the beard is affected, are sometimes gravely perturbed by fears of impotence ; this fear may or may not be correlated with a fundamental psychological ætiological factor. In the popular mind the only correlation between loss of hair and impotence lies in the story of Samson and Delilah :

> "If I be shaven, then my strength will go from me, and I shall become weak. . . . And she made him sleep upon her knees; and she called for a man, and caused him to shave off the seven locks from his head ; and she began to afflict him, and his strength went from him".

It has always been of interest to me that in a country which nowadays is not notable for the amount of time spent by its inhabitants in reading the Bible, the story of Samson and Delilah should have made such an impression. I am thankful that as a nation we have not taken Kingsley's story of the Water Babies so much to heart, for you will remember that Tom grew prickles all over his skin when he was unkind to the other denizens of the river.

It may be argued that overlays of anxiety are seldom of fundamental importance but, as a dermatologist, I must allow for them, if not in ætiology nevertheless in treatment. In alopecia areata, for example, a few early words of reassurance concerning sexual potency may remove an anxiety which, if not removed, may influence not only the response to treatment but also the patient's behaviour.

It is extremely difficult to understand how the forces released by emotional disturbance can produce such widely differing eruptions. Becker and Obermayer (1947) suggested that the following should be classified as neurodermatoses :

Generalized idiopathic pruritus.
Localized idiopathic pruritus of the anal area, vulva or scalp.
Neurotic excoriations.
Neurodermatitis (dry and exudative types).
Dyshidrosis.
Idiopathic chronic urticaria and angioneurotic œdema.
Alopecia areata, totalis and universalis.
Lichen planus.
Vitiligo.
Rosacea.

They suggested that sclerodermia, dermatitis herpetiformis and herpes gestationis, chronic recurrent idiopathic erythema multiforme, aphthous stomatitis and the so-called ulcus neuroticum mucosae oris belong to the same group and that burning tongue, acarophobia and dermatitis factitia should be included.

I would agree that certain examples of most of the maladies of the first group may be psychological in origin, but I doubt whether dermatitis herpetiformis, herpes gestationis and ulcerative stomatitis are psychogenic, and in fairness to Becker and Obermayer it is only right to say that the results of recent investigations may have caused them to change their suggestions concerning these processes. However, one must add that attacks of psoriasis, seborrhœic dermatitis, eczema, lichen planus and dermatitis herpetiformis may be determined in predisposed persons by psychological stress.

Because dermatological nomenclature is execrated by all who have to consider it, and because some may be uncertain of the exact appearance of the maladies to which reference has been made, I propose now to give brief descriptions or explanations of a few of them and at the same time attempt to emphasize the diversity of their manifestations. In pruritus, a complaint which may be psychological in origin or due to a variety of physical causes, there are no visible signs of a primary eruption; the symptoms are a fremitus of uncertain origin and the nerve tracts involved are still undecided. Alopecia areata, or "patchy baldness" which Becker and Obermayer include in their list of neurodermatoses, is a malady in which the skin of the affected area is soft and white, with no palpable change except loss of hair. In contrast, one may consider dyshidrosis which is characterized by the appearance of an acute, symmetrical, itching, vesicular eruption affecting the hands or feet, or both hands and both feet. An important feature of dyhidrosis is that the eruption is not associated with marked vasodilatation of the affected area; this contrasts with rosacea in which persistent vasodilatation of the congestive zone of the face is a cardinal feature and which is not associated with vesicle formation but with over-activity of the sebaceous glands, papule and pustule formation, and occasionally with conjunctivitis and keratitis. Further examples of the protean nature of cutaneous manifestations of emotional stress are seen in lichenification ("neurodermatitis") which may be localized or diffuse, the affected skin being thickened and pigmented, its normal lines exaggerated so that diamond-shaped papule-like lesions are formed. Technically in mentioning lichenification in this way, one may be accused of confusing "primary" with "secondary" lesions of the skin, but as one does not desire to cloud the argument with a dermatological explanation, I will ask you to accept the statement—with some reservations—as it stands. Finally, if Becker and Obermayer are correct in including lichen planus in their list, this is an eruption defined by Ormsby and Montgomery (1948) as "an inflammatory dermatosis in which are displayed multiple, small, flat-topped, angular or polygonal papules". These are red or purplish in colour and are seldom seen on the face, scalp, palms or soles. They may appear on wide or on limited areas. Usually their distribution is symmetrical.

These are but a few examples, but I hope they will serve the purpose of illustrating that if emotional disturbance can be an ætiological factor in skin diseases, then the characteristics of the eruptions which may develop are extremely varied.

Wittkower in his published and unpublished work has done much to group dermatological cases so that one can recognize that certain types of psychological trauma may cause certain forms of skin eruption, but we have done little or nothing to explain how these various forms of emotional conflicts *cause* the characteristic skin lesions: how, for example, some man's complexes concerning narcissism cause the vesicles of dyshidrosis to develop without marked vasodilatation on his hands and feet, whilst in some persons conflicts about sex cause vasodilatation of the face but not elsewhere on the body.

This highly selective mechanism of response is a most difficult matter to elucidate and will require the close co-operation of psychiatrists, physiologists, biochemists and dermatologists before its intricacies can be revealed. Their work will be made difficult by the complicating factor of the activities of the endocrine system, a system which is as vulnerable to nervous stimuli as the skin and one on whose integrity the health of the skin depends.

To illustrate the complexity of this interrelation let me refer briefly to the patches of so-called neurodermatitis not infrequently seen on the nape of the neck in middle-aged women just above the hair-margin. These lesions are similar in appearance, symptomatology and histology to the patches of localized neurodermatitis seen on other areas in persons of almost any age and of both sexes, but neurodermatitis affecting only the nape is rarely seen in men as a single entity as it occurs in women. It is a malady of the menopausal and post-menopausal years, and if there is a psychogenic factor it is usually well hidden. Possibly the major factor is an endocrine one acting in a person who is usually a "seborrhœic subject". I suggest that neurodermatitis of the nape should usually be referred to as lichen simplex chronicus and not as "neurodermatitis".

In the elucidation of the dynamics of the true neurodermatites it seems probable that the technique of hypnosis will be valuable in producing in suitable volunteers wheals, vesicles, bullæ and other lesions, for the greater ease of investigators in this subject. The hazards of environment, infection, infestation, blood dyscrasias, toxins, poisons, gross neurological disturbances and allergy have all been studied widely and although our knowledge of these matters is far from complete we have a fair understanding of their bearing in dermatology. Now is the opportunity for us to unravel the interrelated mysteries of endocrine and biochemical reactions and the effects of nervous stress. But I would like to sound one obvious note of warning; whilst in several maladies (pruritus ani and pruritus vulvæ for example) the primary ætiological cause of the skin eruption may be psychological, in many other maladies some psychological abnormality is but one of a series of factors associated with the cutaneous lesions; unless all of these factors are discovered and set right as opportunity serves, the progress of the case will not be satisfactory. The need—as I see it—is for team work.

Psychiatrists tend to forget, for example, that an eczema may be psychogenic in origin but the symptoms and signs may be perpetuated by mechanisms of infection, auto-sensitization and superimposed contact dermatoses which the patient's mind cannot control. If these secondary effects are not dealt with at the same time as the primary psychological cause, the patient—although he co-operates fully with the psychiatrist—may continue to suffer severely from eczematous eruptions. So I suggest that in dermatology—as in many other branches of medicine—the role of both parties, psychiatrists and dermatologists, should be the role of players in a team, and in that team we would do well to include the biochemists.

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Dr. Eric Wittkower :

Since my appointment as Psychiatrist to the Skin Department at St. Bartholomew's Hospital over 400 patients suffering from eczema, acne vulgaris, rosacea, pruritus, pompholyx, psoriasis and from many other disorders have come under our observation. Only preliminary observations and tentative conclusions derived from our findings, rather than statistical data, will be presented in this paper.

General considerations.—The skin and its appendages are used as means of attraction; they also serve for self-display and self-decoration, i.e. for exhibition. The skin is interposed between a person's inner world and outer world and as such it is in contact with both. It would appear that emotional conflicts which manifest themselves on the body surface cannot be very deep-seated; in colloquial language the term skin deep is used as equivalent to superficial.

The skin is an organ of emotional expression. Vasomotor changes of the skin indicate feelings of fear, anger and shame. Perspiration and cutis anserina are normal emotional responses to fear.

On the perceptory level the skin conveys temperature differences, pain, affection, tenderness and sexual stimulation—some areas more than others.

The contention will be made in what follows that exaggerations and distortions of the psychological mechanisms just described form the basis of many skin disorders.

It is conceivable, as Hodgson suggested, that constitutional differences in skin structure exist. These factors and many others have to be taken into account in answering the questions why the skin has been chosen as the site of disease and why, in any given case, the specific skin malady developed.

Specific syndromes.—The clientele of dermatologists consists of patients who complain of

abnormal skin sensations, and those who display abnormal skin manifestations. To these two main groups a small group of patients may be added who, owing to psychiatric illness, believe that their skin is diseased when it is not.

I shall discuss pruritus vulvæ and pruritus ani as representative of skin sensations, and eczema and rosacea as representative of skin manifestations.

Pruritus vulvæ.—In the absence of definite local causes, sexually well-adjusted and happily married women do not develop pruritus vulvæ. Its very presence suggests that something is amiss in their married life and, that consciously or unconsciously they do not like their genitals or regard them as bad, dangerous or contemptible. Otherwise they would not damage them by scratching. These attitudes may be due to feelings of guilt over misconduct, repugnance to sexual intercourse with their husband, or repudiation of their femininity altogether.

On a superficial and aphoristic level I have learned to classify pruritus vulvæ patients into the shouldn'ts, the won'ts and the can'ts, i.e. those who feel guilty over an illicit love affair or thoughts of infidelity—the shouldn'ts, those who feel duty bound to cohabit with a man whom they loathe—the won'ts, and those who are denied sexual gratification or fertility for a variety of reasons—the can'ts.

At a deeper level, one can discover in many of these patients a revival of guilt over infantile incest phantasies. There is, for instance, in our series, a young woman who after the death of her first lover had resigned herself to a marriage to a man 25 years her senior. From the start sexual intercourse was impossible on account of intense soreness caused by the scratching effects of vulval irritation.

I find it rather difficult to understand how hydrochloric acid medication, as has been suggested by some gynæcologists, can be of any help to relieve the emotional conflicts of these patients. The situation is somewhat different as regards vulvectomy which at least removes—cuts out—that part of the body which these patients, unrecognized by themselves, try hard to damage.

Pruritus ani.—Freud, Abraham, and Ernest Jones described character traits based on compliance with or opposition to infantile bowel training—orderliness, pedantry, persistence, obstinacy, meanness and many others. If, as in the bulk of our pruritus ani patients, these characteristics are present to a neurotic degree, the term anal character has been applied.

If psychosexual development has not reached full genital organization, or if, as in others, a regression has taken place from the genital to the anal developmental phase, immature forms of sexual gratification—auto-erotic or allo-erotic—are to be expected and actually found. Thus, one of our patients—and he is typical of many others—derived a pleasure which had an orgastic quality from scratching himself in the anal region, while another patient invariably suffered from anal irritation when in business negotiations he felt overwhelmed by the acumen of his opponents. Still another, describing the onset of his complaint stated that suddenly he felt transformed from a man into a woman. Basically the mechanism does not differ in women from that in men. Abraham has pointed out that women with pronounced anal characteristics displace libido from "in front" to "behind" and express by this process of displacement their wish for a change of sex. All our female patients were frigid : disorders of sexual function were common in our male patients.

Eczema.—Irrespective of how many and which other factors are of relevance to its ætiology endogenous eczema is a disease which occurs in emotionally insecure individuals. Whether they had been spoiled or ill-treated as children, a majority of our patients felt that they had not had their fair share of affection and were apt to carry over into adult life an undue, childlike dependence on either of their parents or both—usually the mother. Their need for affection, attention, and protection may find overt expression in the form of submissiveness, or display of helplessness. Or, by way of over-compensation, their need may be concealed behind ambition, self-drive, self-assertive or provocative behaviour; not infrequently lack of self-confidence and of self-reliance proved a serious handicap in their social relationships and occupational achievements.

Any situation which endangers or shatters the delicately balanced sense of security of these individuals may precipitate the onset of eczema or of relapses—in particular the loss of a key figure from the patient's environment.

No conclusive answer can yet be given to the question why some individuals develop eczema when they do, while others in a similar set of circumstances enjoy excellent health. There is good reason to believe that a constitutional predisposition to allergic disease and either a constitutional or acquired low capacity to tolerate frustration play a part.

In a few atypical cases the localization of eczematous patches seemed to be symbolically determined. Examples of this kind are eruptions on the wedding-ring finger during marital

infelicity, on the manipulating finger following an extra-marital affaire and at the umbilicus after the death of the mother. As regards the classical distribution, Jelliffe has pointed out that the flexural surfaces are the embracing surfaces and has suggested that the exuding skin aspires to caress, or to be caressed. The skin is the organ of interpersonal contact, and contact, with its implied sense of security, has been shown to be the crucial psychodynamic need of eczematous individuals. In exhibiting his eczema the patients adopts the position of the supplicant, while the weeping of the eczema, like the weeping of a child, reinforces his appeal. He uses no words to explain his need, which is displayed by his gesture; indeed the need may date from an early period before he had words to use.

Rosacea.—Patients suffering from rosacea are usually shy and diffident. Any situation which brings them into the limelight frightens them. They are afraid of losing the affection or sympathy of others because they cannot endure, without anxiety, lack of appreciation, even in those to whom they are entirely indifferent.

Their feelings of inferiority and of unworthiness arise from a deep-seated sense of guilt, the real source of which they are unable to place or to define. To deal with it they use two mechanisms: they either project their presumed badness into the outer world and develop ideas of reference or paranoid ideas, or they try to get themselves into the good books of their environment by means of confession.

Not infrequently—and often under a flood of tears—rosacea patients relate some thoughts or actions to which they attribute their spots and blotches—such acts as masturbation, sexual misconduct, or imagined rudeness. Alternatively, an occasional flush of their cheeks, as certain topics are touched in the course of the diagnostic interview, may belie their uncalled-for protestations of innocence.

The evidence obtained suggests: (1) That rosacea is equivalent to a permanent blush, i.e. represents a manifestation of guilt; (2) that the urge of these patients to disclose minor or major delinquencies arises from a need for punishment; and (3) that their urge to confess is coupled with, and counteracted by, fear of the consequences of their confession. If they are enabled to define their feelings of guilt, to place them where they belong and to verbalize them, the rosacea usually disappears, sometimes dramatically.

Psychological treatment.—In all, 74 patients, suffering from the four skin diseases discussed, were treated by psychotherapy. The treatment was carried out along analytical lines similar to the principles laid down in Felix Deutsch's "Applied Psycho-Analysis". The psychotherapist concentrated on those aspects of the personality which were regarded as essential for the symptom formation.

60 out of the 74 patients taken on for treatment have benefited by it. 52 of the 60 successfully treated patients could be followed up, at least three months after termination of treatment. Of these 35 had maintained their improvement or had continued to improve. Of the four skin diseases discussed, rosacea responded best and pruritus ani worst, to brief psychotherapy.

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Dr. H. J. Shorvon:

Considerable work has been done in recent years on psychogenic factors and psychological precipitants in the ætiology of some skin disorders and attempts made to assess the types of personality liable to develop such disorders. Psychiatrists have devoted little emphasis to treatment, and have only so far treated such cases by systematic long-term individual or group psychotherapy. I became interested in short-term methods of treatment applicable to larger numbers of patients and over a shorter period of time, when I found that tension, from whatever psychological cause, was a common factor in patients referred to me by skin departments as being resistant to the usual forms of therapy. Effective emotional release, therefore, appeared to be an essential of treatment and to facilitate this I adopted drug "abreactive" techniques.

Abreaction is here used in the sense of recalling and re-living emotional experiences, and the more violent the abreaction the more successful the treatment. "Traumatic" incidents and ideas may thus lose their emotional tone and so cease to worry the patient. At the time of Dunkirk, Sargant and Slater (1940), recognized the value of this procedure in the treatment of acute war neuroses when using intravenous sodium amytal. Later it became evident that the more long-standing the traumatic events the more difficult it was to produce a satisfactory

abreaction under intravenous barbiturates. Sargant and I found that we could frequently accomplish this under ether; the technique is described by us in previous papers (Sargant and Shorvon, 1945; Shorvon and Sargant, 1947). The important factor is the emotional excitation produced rather than the accuracy of the abreacted material. It is not necessarily essential to abreact specific incidents or uncover all traumatic incidents, and a great release and relief of nervous tension may even follow a non-specific abreaction.

In the past four years we have also tried other drugs, particularly intravenous "methedrine" (d. methyl phenyl isopropylamine), or an inhalation mixture of 30% carbon dioxide and 70% oxygen as first described by Meduna (1948). 30 mg. of methedrine intravenously produces a clarity of mind, boisterousness, loquaciousness, euphoria and emotional facilitation which is not usually intense but is much more prolonged in its effect than other methods of drug abreaction. One can say that it produces a prolonged moderate excitation in full consciousness. The patient's inhibition and reserve are often swept aside so that much significant material may pour out in a short time. The pressure of talk may continue in this fashion up to twenty-four hours or so. Explosive emotional outbursts may occur, such as during the breaking up of an amnesia.

Inhalation of a carbon dioxide and oxygen mixture is generally milder in its effect with, in successful cases, a gradual relief of tension after repeated treatments, thus ameliorating, but not often curing, the skin disorder. At least 20 treatments are required, for which the patient attends two or three times a week. An abreaction may occur before the patient loses consciousness or as he is coming round. It is a safe, rapid method, and requires a minimum of preparation. In brief, the patient breathes in and out of a bag controlled by a spring valve. The 30% carbon dioxide and 70% oxygen cylinder is connected to the bag via a decompressing valve and flowmeter. Consciousness is lost after some 10 to 30 breaths, as a rule, and this is frequently preceded by a suffocating feeling which may cause apprehension and require preliminary sedation with barbiturates. As a rule, the mixture is inhaled until there is a generalized muscular twitching, and the patient is then allowed to come round.

In treating skin disorders I have used all these methods, singly or in combination, accompanied by superficial psychotherapy and discussion of the patient's life situation. Environmental, domestic, and occupational difficulties are, of course, eased where possible.

The choice of drug depends largely on the personality and past history of the patient, and the occurrence of psychological trauma before the onset of the skin disorder. Frequently a history of psychological trauma is related for the first time in the course of an exploratory abreaction. Broadly speaking, skin patients are either ruminative obsessionals (some with hysterical features) or hysterics (many with obsessional trends) or excessively anxious individuals. The obsessional patient is the most difficult to treat as he ruminates on everything said and cannot relax. Attempts at producing an abreaction under ether or carbon dioxide usually fail, even if the patient is first relaxed by a preliminary intravenous injection of barbiturate. Such patients may be helped by treatment with intravenous methedrine which tends to break down their resistances and allows them to disclose material they are hardly likely to do otherwise. The abreaction may be intensified if, at the more critical points of the recital, an ether mask is applied. Some care must be taken with obsessionals who are paranoid, as these traits may become more prominent. I give 6 grains of sodium amytal by mouth some hours after a methedrine abreaction to sedate the patient, but find that at times this helps the disinhibiting effect of methedrine and the patient goes on chatting, often with increased vigour.

Hysterical and anxious patients do well with ether abreaction alone. The obsessional with hysterical features or emotional instability may also respond. The gross hysteric, however, may occasionally, instead of abreacting, dissociate repeatedly. Carbon dioxide inhalations have a decided value when used to round off an ether abreaction in such cases.

I have treated successfully by repeated abreactions cases of prurigo, exudative neurodermatitis, atopic and non-atopic lichenified neurodermatitis, neurotic excoriations, dermatitis artefacta, hyperhidrosis, pruritus ani, pruritus vulvæ, urticaria, angioneurotic œdema, rosacea and dermographism, and relieved the subjective symptoms of psoriasis.

I will quote briefly five cases illustrating outstanding points in the ætiology and personalities, types of reactions, and choice and results of treatment of particular skin disorders.

Pruritus vulvæ.—Such cases, in a pronounced psychogenic setting, are notoriously difficult to treat. The pruritus is often masturbatory, or a defence against sexual intercourse, particularly if it begins after childbirth. Patients often have a fear of pregnancy or marriage as a result of earlier sexual traumata and frequently show hostility to their children. They are usually immature, obsessive hysterics, and are resistant to the idea that the pruritus may serve a useful purpose.

A patient of 25, complained of intractable pruritus vulvæ which began after marriage four years ago and became severe after childbirth two years later. X-ray treatment gave

only some days' relief. Numerous other therapies met with little success. Her father was very strict and her mother had a "filthy" temper and she attributed her fear of pregnancy to her mother's stories about childbirth. During the early years of marriage there were many sexual difficulties and dyspareunia. She was treated by weekly ether abreactions and during the third abreacted violently over a sexual trauma at the age of 10. This had been repressed, but on her honeymoon unsuccessful attempts at intercourse produced similar reactions of disgust as she experienced when assaulted. The pruritus was relieved following this abreaction. Gradually, with further emotional release, when discussing her mother, childhood, and fear of pregnancy, her condition improved and intercourse became satisfying. She suffered a slight relapse when the family brought pressure on her to have another child.

Pruritus ani.—These patients often show strong obsessional trends, and early homosexual experiences may focus attention on the site of the lesion.

A male patient of 23 complained of pruritus ani and an irritating rash (neurotic excoriations) of the bathing drawer area for four years, which began on Army service. He was an obsessional who denied homosexual traits. The irritation failed to respond to the usual therapies.

Two attempts at abreaction under ether failed. He improved following twenty-five carbon dioxide – oxygen inhalation treatments but was not cured. Intravenous methedrine was then tried and uncovered his brother's homosexual practices with him in adolescence. After the possible connexion between his symptoms and his brother's acts was explained the patient showed some improvement despite considerable guilt. During the second methedrine abreaction he admitted to frequent acts of sodomy with his brother about the age of 13 and asserted that he had long forgotten about it. The pruritus started after embarkation leave following an isolated act of sodomy with his brother after an interval of years. The condition practically cleared after this abreaction.

Generalized pruritus and lichen planus.—After effective abreactions patients piece together past events more easily, and sometimes, with the dramatic breaking up of an amnesia that has held firm for many years, there is equally dramatic resolution of the skin disorder.

A male patient of 49 gave a history of skin irritation for thirty years and generalized lichen planus for three years. He was a frustrated, hostile obsessional who had been invalided out of the first world war with D.A.H. and was doing inferior work, unworthy of his abilities. There was some symptomatic improvement after two mild ether abreactions but during the third he suddenly abreacted violently, and an unsuspected amnesia of some days' duration in the first world war was resolved. This treatment resulted in a marked mental and physical improvement, but there were many details to elucidate and it required six further abreactions for the skin trouble to clear completely. Thus a pruritus of thirty years' duration which began after an amnesia persisted until the amnesia was uncovered. It is interesting that his lichen planus cleared with abreaction as it is a condition considered by some authorities to be of psychosomatic origin.

Hyperhidrosis.—A male patient of 27 complained of headaches and bursts of sweating of the head and neck lasting about half an hour at a time, which had a sudden onset whilst drinking tea eight months ago. He mentioned that he had a persistent amnesia for events at Anzio in his first and only battle after a shell burst. Attempts to break through the amnesia under intravenous amytal, ether and carbon dioxide failed. After an intravenous methedrine he became very restless and the amnesia unfolded with a profound emotional release. He described his state of tension when ready to go into battle. At zero hour he could stand it no longer, and against orders, he looked out of the trench, exposing his head and neck. There was an immediate shell burst and he "collapsed". This incident may well account for the odd distribution of the sweating and it is of interest that references to fighting in Italy were taboo in his home, but eight months ago, at a tea party, his mother talked at length about it. The hyperhidrosis cleared.

Exudative and lichenified forms of neurodermatitis appear to be precipitated by frustration, anger, hostility, grief, disappointment or unaccustomed responsibility. Repeated shocks and anxieties may result in repeated attacks. The general release of anger and aggression under ether and methedrine, alone or combined, often produces a rapid amelioration of chronic eczematous reactions which have more or less defied the usual treatments.

A male patient of 50 complained of eczematous eruptions of the forearms, flexures of the elbows, face, neck and scrotum. The skin was bright red and infiltrated, and he was depressed, tense and sleepless. He worked with obsessional intensity for twenty years to reach a desired status, and learnt to control the violent tempers of his youth. After much frustration he gained his promotion. He now experienced two severe shocks. His new boss was a man he loathed and his only child failed an important examination. The skin rapidly

cleared after four ether abreactions, rounded off with carbon-dioxide inhalations. The emotional release over his chief and the examiners was intense. Some weeks later his son was killed in an air crash and he relapsed. There was only a slow improvement this time with ether and carbon-dioxide abreactions. The patient's favourite brother was then killed in a street accident, and the skin disorder flared up again. The treatment was discontinued because of depression, but on resumption he abreacted over an administrative muddle with his son's effects, and the skin condition again showed some improvement. He finally cleared altogether after two injections of methedrine.

The cases quoted have remained well for at least six months.

I have so far treated 50 patients, all referred by dermatologists. It is not claimed that all have responded to treatment and a full account of a consecutive series of cases will be published shortly.

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Psi Phenomena and Psychiatry

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THERE is a long historical relationship between psychiatry and the study of psi phenomena. Parapsychology, the science of psi capacities, those functions of personality that defy physical explanation, might almost be called a historical derivative of psychiatry.

If we extend the history of psychiatry back to Mesmer's time, we find the problems of parapsychology closely intermingled—or we might better say, confused, as they were at that time—with those of psychiatry. From the beginning of mesmerism, we find associated with it accounts of phenomena of what is now called extrasensory perception or ESP (a capacity more commonly known as telepathy and clairvoyance). The association was so close that for a long time these phenomena were taken to be incidental features of the mesmeric trance or somnambulism. Mesmer himself mentions these phenomena of ESP almost casually; Goldsmith [14] quotes him as saying: "Sometimes through his inner sensibilities, the somnambulist can see the past and future."

Among his followers—though never so with Mesmer himself—these phenomena of ESP threatened for a time to become the dominant aspect of the mesmeric manifestation. This became particularly true following the discoveries of the two Puysegur brothers, especially the younger, Count Maxime, that some subjects demonstrated what appeared to be clairvoyant awareness of the illnesses and physical conditions of fellow patients. This discovery led to the practice of having mesmerized persons attempt to diagnose disease, presumably by clairvoyance, a practice that lasted to some extent for at least a century.

Some idea of the degree to which the extrasensory aspect of mesmeric phenomena captured the interest of the day may be gained from the report made by the Second Commission on Animal Magnetism of the French Academy of Science in 1831. In this report, the record of the tests of the clairvoyant powers of the somnambulist makes up a large part of the recorded evidence.

Even though a new Commission only a half-dozen years later blasted mesmerism in general, it did not kill it completely; not only in France, but in Germany and England as well, there continued to be occasional reports of the transcendent mental abilities of the somnambulists. In America, this combination of somnambulism and the belief in psychic powers, along with other elements, gave off various by-products, such as Spiritualism and later on Christian Science.

In the latter half of the nineteenth century when mesmerism had become hypnotism, and a somewhat more experimental approach to the phenomena had been developed, a number of physicians of mental disorders encountered phenomena of extrasensory perception in their practice of hypnotic therapy on hysteria patients. One of the first of these was Dr. E. Azam [1], who observed that his hypnotized patient appeared to experience the taste of substances which the physician put into his own mouth. Dr. A. Liebeault [22] found patients able to perceive visual images that were being experienced by the hypnotist, and

Janet [20, 21], with the collaboration of Charles Richet, demonstrated what was called telepathic suggestion or hypnotization-at-a-distance with the famous patient, Léonie.

Among the more dramatic of the ESP phenomena reported was that known as "travelling clairvoyance". According to Richet [31, 32] Janet attempted to demonstrate this effect by giving Léonie the suggestion in the hypnotic state at Le Havre that she would mentally visit Richet at his laboratory in Paris and bring back an account of what Richet was doing. She cried out that the laboratory was burning, and in fact it did burn to the ground that very day.

But, with the discovery that the capacity for telepathy and clairvoyance was apparently *not* dependent on the hypnotic state, and also with the decline of the use of hypnosis as therapy, reports by physicians of demonstrations of extrasensory perception in hypnotized patients ceased to appear.

Much later, and well into the twentieth century, a number of psychiatrists of the psychoanalytic school took an incidental interest in telepathy, although now without any association between it and hypnosis. The first of these, as far as we know, was Dr. Wilhelm Stekel: He gave considerable attention and emphasis to the importance of telepathic dreams and published his book [38] on the telepathic dream in 1921. In the following year Freud published a paper [13] under the title of "Dreams and Telepathy" in which he considered a possibly telepathic dream from the point of view of psychoanalytic theory. Freud's interest in telepathy persisted, and there were later publications on the subject from him [11, 12], although none that committed him in print to an unreserved conclusion as to the occurrence of telepathy. Jung had participated in parapsychological investigations before the opening of the century, but had not attempted to integrate his parapsychological and psychiatric observations. During the 1920's and 1930's a number of other analysts, Deutsch [6], Burlingham [5], Hollós [16], Róheim [34], and Peerbolte [25], contributed papers on the telepathic dream experiences of their patients. During the last decade another generation of psychoanalytic contributors has taken up the study of the role of telepathic dreams in psychoanalysis. Among these, the more familiar names are those of Eisenbud [8, 9], Ehrenwald [7], Servadio [36], Fodor [10] and Pederson-Krag [24]. Active psychiatric interest in parapsychology in England is represented by the names of the late T. W. Mitchell and William McDougall (Outline of Abnormal Psychology, New York, 1926), and among the living by those of William Brown and Laurence Bendit [3].

In the *experimental* investigation of extrasensory perception, psychiatry has at least one representative, introducing, perhaps, the beginning of a new era. He is Dr. Hubert J. Urban [41]. Dr. Urban and his assistants, Dr. M. Harrer and Mr. Friedrich Köck, have for a number of years been engaged in the experimental study of ESP in the neuro-psychiatric clinic at Innsbruck.[1] I shall have more to say about their work a little farther on.

It is evident, then, that there has been a fair amount of contact on the part of the profession of psychiatry with the phenomena and problems of parapsychology. Through the years the relationship has changed considerably, but it has not been a growing apart. Recently Dr. Russell MacRobert [23], a New York psychiatrist, conducted a questionnaire survey of psychiatric opinion in the United States regarding ESP and its investigation. Of the 723 psychiatrists that replied, 23% stated that they had personally encountered ESP, and another 17% were uncertain. 68% agreed that the profession should sponsor research in extrasensory perception. Mentioning the MacRobert survey, the editor of the *Psychiatric Quarterly* said of extrasensory perception in the April 1949 number: "This is certainly appropriate territory for psychiatric exploration."

It has, in most instances, taken some courage for psychiatrists to venture into these even more unconventional pathways than those to which they are accustomed, and there never has been a time when parapsychology was conventional. The interest of psychiatrists in telepathy and clairvoyance did much to direct to these phenomena the scientific attention they received during the latter part of the last century, resulting in the formation of the Society for Psychical Research.

But is the connexion between psychiatry and parapsychology anything more than historical? Is ESP or any other parapsychological phenomenon related in any fundamental way to psychiatry? We have already seen that so far as hypnosis was concerned the connexion was largely fortuitous. It was already fairly clear in the 1870's and 1880's that the demonstration of telepathy and clairvoyance was apparently as successful without the hypnotic state as it was with it, and with the introduction of the suggestion theory of hypnosis the conceptions that might have been of interest to parapsychology were abandoned. Through the

[1] A later report, written by Dr. Harrer and Mr. Köck, appeared in *Neue Medizinische Welt* for April, 29, 1950, Vol. 17, 1-8.

years, experimental work in ESP with normal subjects in the normal state led to the abandonment of former views that the state of trance or somnambulism and the use of automatisms and other dissociated states were favourable to the exercises of ESP capacities. However, it should not be regarded as a completely closed issue that there is no sort of alteration of consciousness that can favour ESP performance. Possibly an important connexion may be found between some type of modification of consciousness and the functioning of ESP, even though nothing has been found thus far to support the early association of ESP with mesmerism. Also, the old association of ESP capacity and hysteria went the way of the former linkage of hypnotizability and hysteria to which it had owed its origin.

There is, in fact, *no evidence as yet of any positive tie-up of ESP ability with pathology of personality*. In this connexion let us first look at the collection of spontaneous experiences of apparently parapsychological nature to which we owe the original interest in the subject. From this case material we find that those individuals who have unexplainable experiences of telepathic or clairvoyant nature appear to represent a normal sample of the population and do not show an outstanding amount of instability. There are cases sent in from persons who are obviously unbalanced, but these cases are neither predominant nor typical, and they seldom contain anything of parapsychological interest. A number of persons who suffer from delusions of persecution have claimed that telepathy is the means by which they are being persecuted, but there is no evidence that these claims of persecutory telepathy have any foundation in fact.

The type of alleged psychic manifestation that would appear most likely to involve maladjustment is what is known as the poltergeist case, usually associated with the presence of a single individual, most often an adolescent. If any of the poltergeist reports can be taken seriously, there is obviously evidence of some sort of serious maladjustment; but it is difficult from the present state of knowledge to tell who or what is maladjusted.

When we turn to the *experimental* studies of ESP made on patients in mental hospitals, we find that these confirm the general impression gained from the study of the spontaneous cases, that thus far no association has been found between psychopathology as such and ESP capacities. Four such investigations have been made in American hospitals and, as already mentioned, one at the neuropsychiatric clinic at Innsbruck. In these tests the patient tried to identify the symbols on concealed cards. These cards are standard equipment in ESP tests, and a pack consists of 25, 5 cards with each of 5 simple geometric designs. In none of these investigations were test records obtained that were in any way outstanding. In fact three out of five series gave overall results that were not significantly different from chance. One of these, done at the Hudson River State Hospital in New York, was reported by Shulman [37] in 1938. The patients in only one of the 14 clinical classifications tested gave a significantly positive result. In another study made at the North Carolina State Hospital by Smith and Hull (and still unpublished), significant differences were obtained that are considered of psychological interest, and a third small series by Van Wiemokly [42], carried out at the New Jersey State Hospital, closely agreed with Shulman's findings as far as it went, but the average result of all three are close to the mean score expected from chance, 5 successes per 25 trials.

Price [*see* 29, pp. 260–61], in 1939, at the Ohio State Hospital, tested patients in a broad range of clinical classifications and obtained the general average score of 5·53 hits per run of 25 trials for the work as a whole. She had worked with institutionalized groups earlier, at a State school for the blind and at an orphanage,[1] and had obtained somewhat comparable scoring rates: 5·64 hits per run for the blind and 5·54 for the orphans. Urban and his associates have turned out an average of 5·37 hits per run in their tests with mental patients over the two-year period of 1948–49.

As students of parapsychology well know, the scoring rate of the subject or group of subjects is likely to vary with the experimenter; in other words, interpersonal relations play an important part in ESP tests. This must be expected when delicate psychological processes are being measured. Statistically, the two series last mentioned, that of Price and that of Urban, show significant positive deviations and the chance hypothesis may be rejected. It should be recognized, however, that the experimental conditions necessary for these clinical tests do not permit the elaborate controls that the laboratory ESP tests usually involve. Of the five series with mental patients as subjects, only the Smith and Hull experiment involved the more elaborate safeguards characteristic of the laboratory methods. In all five experiments, however, the level of precaution compares quite favourably with clinical work of any other character, and some findings of value and a fair amount of consistency have come from these studies. We shall come back to them again a little later.

[1] *J. Parapsychol.*, **2**, 273-86, 1938.

Whatever else the experiments in the hospitals show or fail to show, there is no disputing the fact that they do not reveal any connexion between pathology and ESP capacity. On the basis of the evidence, no one would recommend the mental hospital as the place to go in search of especially high-scoring subjects, though, as we shall see, there are other good reasons for desiring to pursue parapsychological research in such institutions.

In addition to the spontaneous cases and the studies made with mental patients, there is a third source of information bearing on the question of the possible relation of mental health to psi capacity; it lies in the area of personality studies made on *normal* subjects who have participated in ESP tests. The results of these studies favour the view that if there is any difference at all, those with the better mental health do better scoring in the tests. For example, Schmeidler [35] has generally found in her Rorschach studies of ESP subjects that the better-adjusted individuals give the large deviations in ESP tests. The studies which she has made with other personality tests to some extent support this finding, although she has not gone far with them as yet. The Rosenzweig frustration test and appraisal of the subject's work attitudes have been correlated with the ESP scores of the subjects, and the results suggest that those who, in general, show the least tendency to maladjustment are likely to give higher scores in the ESP tests. There is some unpublished work by Lawrence and Humphrey in which ESP performance was correlated with the subjects' scores on the Bell Adjustment Inventory. A positive relation between good adjustment and good performance in the ESP test was suggested. Studies made with the Stuart Interest Test, both by Stuart [39] himself, and, after his death, by Humphrey [19], show that individuals who are more moderate and less extreme in their patterns of likes and dislikes or even in their pattern of indifference give better score records in ESP. Such moderation is presumably the more healthy reaction.

In the main, these results are only suggestive, and it is recognized that they may deal only with superficial factors such as inhibiting states or functions, rather than with the actual amount of ESP ability which the individual possesses; we can say, at any rate, that on all the lines mentioned, there is a complete absence of any tie-up of ESP success with neurotic traits or psychotic tendencies. Thus far nothing has indicated any special linkage between psychopathological and parapsychological functions.

There is one misconception that needs clarification. Some of the subjects who have scored at an unusually high level, at least for short periods, seem to show one unusual characteristic: While no one has been able to make a psychological study of these exceptional individuals, the impression is gained from the reports that they have in common an exceptional amount of sensitivity or responsiveness, almost of easy excitability. This may be important to their high scoring. It would seem that the subject's capacity to let himself go readily and respond with high spontaneity to the challenge of the test should enable him to escape the restraints of fixed habit and intellectual set.

Such a temperament in itself is not pathological, but the fact that it may easily be associated with neurotic symptoms may have led to some unwarranted speculation and generalization. So far as we know there is no other common trait which distinguishes these exceptional individuals, if, in fact, they have any common distinguishing characteristic.

To say, then, that something is parapsychological does not imply that it is in any way psychopathological and the statement is just as true with the two words interchanged. However closely the two fields have been related historically, they are distinct, and so far as we can tell, independent of each other.

They do, however, have a long common frontier and a large area of common interest. Probably the main point in common to parapsychology and psychiatry is the fact that both fields deal largely with *unconscious* mental life. The phenomena with which parapsychology deals and which (at the suggestion of Thouless and Wiesner) we have agreed to call *psi* phenomena, might be described as almost completely and irrecoverably unconscious. Indeed, it may be that psi phenomena are the only truly unconscious ones that we know in psychology. Experiences which have been more familiarly termed unconscious might be distinguished as not in present consciousness but more or less easily recallable to consciousness, at least with professional help. The typical extrasensory perception is something that has not in itself been consciously experienced by anyone at any time so far as we know.

To illustrate the complete unawareness of ESP experiences I will recall the case of Riess's [33] subject. He reports that she averaged over eighteen hits per run of twenty-five trials (with the usual mean chance expectation of five) throughout a series of seventy-four runs, one run even having a perfect score of twenty-five. After a period of illness covering several months a second series of ten runs was made, and this gave an average of only a small fraction over five hits per run, the score average expected from chance alone. The remarkable thing is that the subject had no different impression of success during the high scoring than while she was getting only the chance scores. In other words, she was completely unconscious

of her rate of success even at its highest pitch. Her conscious experience was totally unrevealing with regard to the operation of ESP as a process. She thought of one of the five symbols for each trial but was entirely unaware as to why that particular judgment was made. If she had been questioned she might have given a rationalized explanation for the choice of a particular symbol, or she may not; she may just have said that she was guessing, or that she chose a given target symbol because she had a more vivid mental image of it. Such replies are the more common ones, but quite obviously no one has thus far shown any reliable introspective awareness of success in the experimental work on extrasensory perception.

This unconsciousness of ESP has already been found to produce a number of exceptional effects, and there may be others that are still eluding us. One of the best known of these is the effect sometimes shown of unconsciously avoiding the target instead of identifying it, thus producing a score *below* that expected from chance, and resulting in a *negative* deviation instead of a positive one. Another effect that is ascribable to the unconsciousness of ESP, at least in part, is what is called the position effect. As the name suggests, this effect deals with patterns of successful scores that are related to the positions of the trial in the run or column on the record sheet. Quite unconsciously a subject may, for example, score at a high rate at the beginning of the run and, perhaps, again at the end, but he may drop to a chance or even a negative level of scoring in the middle. Unconsciousness, too, has produced an effect called *displacement* (the term introduced by the late Whately Carington), the tendency of the subject to hit the targets before and after the one at which he is aiming. Recently at the Duke Laboratory still another effect of unconsciousness has been encountered by Cadoret and Pratt [26]. They found that some subjects consistently mistake one symbol for another and produce a reliable type of missing even while they are consistently hitting certain other symbols.

Using mechanical aid in carrying out extensive analysis, Pratt and Foster [27] of the Duke Laboratory have recently found that the subject's displacement and consistent missing combined may produce a highly complex pattern of significant effects. Among other curious results they find that the subject displaces differently before and after *hits* (i.e. successful calls) than before and after *misses*. Working with very long series as they are, the findings are based on data that possess a high order of significance. This systematic wandering up and down the run of target cards and off on to the wrong symbol is quite understandable as a product of the introspective blindness that seems to be a universal characteristic of the process. Presumably if any clear introspective awareness of the occurrence of ESP were to be achieved, these peculiar effects would be eliminated and a high order of conscious control, as well as utilization, of the process would be possible. The range of possible consequences of such utilization would be very great indeed.

We may very well learn something about unconsciousness as such from the study of these psi phenomena—something of general psychological value. It is apparently necessary to convert an ESP response either into imagery or into a motor response in order to register it. This suggests the hypothesis that sensory perception and its derivatives constitute consciousness and that ESP reactions are the normal, *un*conscious counterpart of the conscious sensory phenomena. In that case there might be nothing to do about the unconsciousness of psi phenomena; that is, nothing that will bring the operation of psi within the scope of introspection.

We have, however, many spontaneous psi cases reported to us in which an individual is strongly convinced he has had a veridical experience of a remote happening. These experiences are too familiar to require illustration at length. No case of this type is more common than that of the mother who receives an impression, perhaps by way of a dream, that her child is in danger or has been killed. In some instances she is so strongly impelled to act on the strength of her impression that she does so in spite of the ridicule or resistance of those around her. Sometimes the person concerned is so moved by his experience as to travel hundreds of miles or otherwise go to great trouble.

While we do not consider such anecdotal or clinical material as capable of providing any final order of evidence, we may well learn from it something of great use to the research field. The value of such cases is mainly in the planning of research, in which connexion they have already proved their worth. It is true, they do not in themselves constitute introspective experience of extrasensory perception comparable to our introspection of sensory experience. The nature of the feeling of conviction or the experience of this certainty of the knowledge conveyed is in itself a problem, but it looks like an intermediate step in the direction we wish to take in coming to grips with what is taking place in ESP. An extensive research programme is now under way at Duke Laboratory, under Dr. Pratt's supervision, to attempt to discover whether the subject changes his pattern of calling when he makes a hit. The subject is not told, of course, until the end of a run on which trials he makes correct calls. Accordingly if he should by any sort of change in his calling procedure show some consistent reaction to

success, we would know that at least on an unconscious level there is a reliable register of success. We might, then, with more confidence attack the problem of getting this registration across the threshold to consciousness or, at least, getting it into the range of control.

Pratt is at present working on old records of ESP tests made many years ago and is looking for effects only in the recorded call sequence, but similar studies should be made while the test is actually in progress with a view to catching in action any accompanying physiological effects that might register response to success. The work of Brugmans [4] carried out nearly thirty years ago, in which he used the galvanometric skin response test showed a close enough relation between the response and success in an ESP test to justify following up that method.

Perhaps I have said enough about the unconsciousness of the psi processes to indicate the common need of parapsychology and psychiatry for a depth psychology. It seems probable therefore that developments of real significance in getting at the unconscious levels of mental life will be as helpful to us in parapsychology as they will be to psychiatry.

It is too early yet to draw close parallels between the fields of psychiatry and parapsychology but areas of possible overlap from the standpoint of unconsciousness may be suggested. The work of Urban and his associates suggests a close relationship of the two fields. These investigators report improved scoring in ESP tests following electro-shock and insulin-shock, and during narcoanalysis. If this work is sufficiently confirmed, it will strongly indicate that these methods are removing the inhibitions that we think are responsible for lowering the performance of the subject in the ordinary ESP test.

In parapsychology we have stressed the importance of having a game-like test and of creating a play atmosphere to help the subject forget that he is being tested. Probably the main value of such procedure is in breaking up the rational habits that normally guide his decisions. Success in an ESP test appears to depend upon securing a certain spontaneity in the ESP judgment. Perhaps this is why a long series of trials in close succession tend to produce a decline in scoring rate for most subjects. On the side of psychiatry we find Moreno also laying great stress upon the importance of spontaneity in his technique of psycho-drama or play therapy. The more successfully the patient enters into the dramatization of his conflict the more successful he is in getting rid of it.

Hypnosis as a method of depth analysis and therapy is much disputed, and its value, likewise, for parapsychological investigation is a problem for research. Perhaps we may say that in both fields enough has been claimed for hypnosis in the past to justify continued interest, provided the necessary research can be done to guide our interest intelligently.

It is clear, at any rate, that historical continuity is not the only common interest which psychiatry and parapsychology have. As fields dealing with unconscious mental life, they are also closely related; but the relationship does not end here. Another large sector of common frontiers which the two fields share is the dependence on what is variously called personality psychology, character psychology, the psychology of individual differences, and the like. Certainly personality traits and the general structure of the personality are important for both fields.

It will be recalled that Shulman obtained different ESP results for the various clinical classifications with which he worked at the Hudson River State Hospital. Of the fourteen classifications, the lowest score average was given by the involutional melancholia group consisting of nine individuals tested in a total of 290 ESP card runs. These patients' average score, which was below the mean chance expectation of five hits per twenty-five, was 4·72. Shulman's findings on melancholia were closely approximated by Van Wiemokly, who did not know of Shulman's results at the time. Price found the involutional melancholia patients scored at the lowest level. Smith and Hull did not work with the melancholia patients.

Although the four investigations mentioned above yielded quite similar results, there is an interesting difference between them. Price's melancholia group gave a positive score average (that is, above mean chance expectation of 5·00), whereas the same group for Shulman and Van Wiemokly gave significantly negative deviations taken together. Individual differences in subject-experimenter relations, the atmosphere of the test situation, the type of tests, general hospital atmosphere, &c., can all play an important part in determining this score level. The important thing in this instance is the score level of the melancholia group, relative to the score levels of the other classifications. It is, therefore, worth noting that in all these explorations in which melancholia patients were tested, that group fell at the bottom of the scale of clinical classification.

In three out of the five ESP investigations made in mental hospitals, patients diagnosed as manic-depressive depressed were tested for ESP ability. Shulman tested twelve patients from this group and obtained his highest score average with them. The fact is, depressives gave a significantly high positive deviation. Price had only three patients of this classification as compared to Shulman's twelve, but their average was the highest she obtained for any of the major classifications (exceeded only by patients with simple behaviour disorders).

Smith and Hull set out to make a comparison of depressed and manic patients and obtained a positive deviation for the depressives and a negative one for the manics with a significant difference between the two, a difference also found by Shulman.

These studies, while not sufficiently well controlled to allow us to draw hard and fast conclusions, afford a clear suggestion of the importance of personality traits and attitudes in relation to ESP test performance. Studies made on normal subjects have given strong support to this impression.

The relationship that has perhaps the best experimental foundation is that of the effect of attitude in ESP scoring as established by Schmeidler. She has repeatedly shown that favourable, as contrasted with unfavourable, attitudes toward the possibility of the occurrence of ESP are associated with significant effects on the scoring level. The "sheep" or favourable subjects, tend to score above the chance average, while the "goats" tend to score below. Very probably we are dealing here with a superficial effect which we may call a "sign factor", denoting an ESP response which reflects the subject's attitude toward the test. Hypothetically, he may call the cards correctly, in order to help bear out the experimenter's theory, or he may call them incorrectly in order to disprove or reject it. In either case, the response is one of ESP; the subject's attitude merely determines the form it will take. I have mentioned Schmeidler's further studies with the aid of Rorschach analyses, and the finding that the well-adjusted and non-constricted subjects gave the largest effects in ESP tests; as would be expected, the "sheep" in this subgroup gave the highest score average, while the "goats" with the same personality characteristics gave the largest deviation from the mean in the negative direction. It appears that the well-adjusted, non-constricted subjects have the more ESP ability to register in the tests, but they register it positively or negatively depending upon whether they are "sheep" or "goats".

Stuart [39] showed that the subject's interest pattern could be used as a basis for separating high from low scorers in ESP tests, and Humphrey [19] has followed this up with further refinements. These are now being made the basis for a special personality test designed for the purpose of selecting high and low scoring subjects in advance. Humphrey [17, 18] has also found that the style of reaction of the subject as measured by the form quality of his drawings can be used to effect a significant separation of high and low scoring subjects. In the ordinary ESP tests, the person whose drawing is rated as expansive as opposed to compressive, the one who makes good use of his space and shows good judgment of proportion, seems to adapt more successfully to the ESP test, as indicated by his scores.

These are some of the indications that we, too, in parapsychology are dealing with processes rooted in the personality structure of the individual; we, too, are handicapped by the ignorance that still prevails as to the nature of personality and its organization.

There is yet another area of interest common to both parapsychology and psychiatry, that involving the part played by the nervous system. Quite obviously any effects such as Urban reports as coming from electro-shock, insulin-shock, and narcoanalysis would be relevant to this common ground. All these treatments seem rather markedly to affect ESP scoring rate, suggesting that somehow in this tampering with the cerebral cortex, there was some liberation of the ESP process as measured by the test. If these researches serve only to point the way to an important line of attack, they may be serving a most important function.

They are supported, too, by results obtained in ESP tests involving the use of drugs. While it has been found that heavy doses of the narcotic drug, sodium amytal, depressed the scoring rate in ESP tests, Brugmans [4] obtained an improvement in scoring by giving a moderate amount of alcohol to his subject.

If, along with these observations, we keep in mind the unconscious character of the psi processes and the tendency of the spontaneous occurrences of psi to take place in the dream state, the hypothesis is suggested that psi functions are evolutionally primitive, belonging to structures of the nervous system that are now less dominant in man because of his larger cerebral development. Perhaps we need not suppose a specific localization, but it seems worth while to suggest, at least, that the growth of associative areas affording a basis for rational thought has eclipsed something of the activity on which the functioning of psi depends.

If there is anything in this speculative hypothesis we might expect to find superior examples of ESP in some of the species with less cerebral development. Unfortunately, we cannot turn to any extensive amount of experimental work for a check on this point. The field of research is too new for that. We do have on record an exploratory study of dogs [2] and one on a horse [30] but it is difficult to get comparative evidence from them, since that would require an equating of the adequacy of the test for the species concerned. Let us for the present consider the anecdotal material available, especially since the whole matter is

purely hypothetical at this stage and the worst we could do would be to conduct an experiment which would show that we had been temporarily misled.

The anecdotal cases which most emphatically challenge attention are those puzzling stories of long-range direction-finding on the part of dogs. Granting the fallacies of human testimony, some of these cases would still seem to be worth taking seriously. Time and again we are assured of the facts in cases similar to this: A dog travelling with his master becomes lost, far from home. The distance may be a hundred miles, a thousand, or even more. In some cases (and for our present purposes it does not matter what percentage) the dog returns home after weeks or months of wandering. Other cases may involve a dog that is left behind when the family moves to a distant State where the dog has never been. Again the distance may involve hundreds or thousands of miles; and, again, there are cases on record in which the dog finds his ungrateful master after wandering for months over a completely new territory. There are numbers of cases like this. They suggest that the animals in question possess a capacity for extrasensory perception far excelling anything that has ever been reported with equal plausibility in connexion with human subjects. The homing dog would apparently have to have an almost continual orientation and a practically perfect reliability in the functioning of its extrasensory powers.

These well-attested cases of the dog make us bold, then, to open a question with regard to homing and migratory movements of a still lower species. There is still no established explanation for the migration of birds, where, as in the flight of the golden plover from Alaska to the Hawaiian Islands, a distance of three thousand miles over open water, great precision in navigation is needed. We have no known principle to apply except ESP. The problem of the homing pigeon has led to theories of a magnetic sense and a capacity to respond to the coriolis force of the earth, but in contrast to the cases of ESP there appears to be no evidence of any response to these forces by *any* living organism. The entire case is pure conjecture. Some of the reports of individual performance by homing pigeons (such as that of the flight of a pigeon from French Indo-China to France) may challenge credulity but, at least, they challenge the adequacy of any known hypothesis other than extrasensory perception. The suggestion has already been made by at least one ichthyologist (Sumner [40]) that perhaps the unexplained migratory movements of the salmon in its return from the ocean to its starting point might involve extrasensory perception.

It is plain that we have here a number of problems for investigation and problems of magnitude that involve a number of professional groups; but here again if I understand correctly there is a parallel situation in psychiatry, in the need to find the origins or foundations of mental disorder, tracing them, if need be, far back into relationships as primitive as those which I have been discussing.

This problem of the evolutionary origin of psi capacities may well receive the greatest contribution toward its solution in the neuropsychiatric clinic. It would seem likely that if parapsychology can sufficiently penetrate the clinic and take advantage of the opportunities offered in the modern hospital with its neurosurgery, neuropsychiatry, and other developments, it would have a rich opportunity to test the general hypothetical picture I have drawn. Having opportunities to work with persons in whom the later evolutionary developments of the nervous system have been temporarily interrupted is not the only requirement, however. Just as we have no way of knowing how much ESP capacity a dog may have until he is placed in the condition or urgent need for it and opportunity for demonstrating it, so must we induce in the subject proper motivation for the kind of response we want to elicit.

While, then, we may hope for expanded research developments into the appropriate branches of animal study, we shall also hope for aid from psychiatry and neurology on what appears to be a frontier of common problems, the exploration of what goes on under the heavy overlay of associative process which our cerebral evolution has brought us.

What significance the findings in parapsychology may have for psychiatry it is too early yet to say. It is only possible now to indicate lines of possible bearing, and go on to the research needed for a better answer. There is, first of all, a question often raised by the psychiatrist himself as to the possible role of ESP, especially of telepathy, in the patient-psychiatrist relationship. The establishment of rapport with the patient is especially important to certain kinds of therapy. If telepathy could enter into this operation it could be very important. Many psychiatrists think it does.

Again the research in parapsychology widens considerably the area with which the psychiatrist may have to deal in his search for explanations and determinants. The spontaneous cases of psi experience which now have some evidential support go far to suggest that a person's mental environment may be much wider than has been supposed by psychology. Evidently there is some psychological linkage between certain people who are closely attached to each other in friendship. The connexion does not often reveal itself in conscious experience, but it is a good question whether there may not be much more integration among friends

than is suspected. This area of possible interpersonal influence could be of immense importance to the health and development of the mind. It is rare that these telepathic relationships become so obvious as to be recognized as disturbances; but cases are fairly numerous in which one person goes through the symptoms of illness or suffering that a close friend or relative is experiencing at the time. If this be so, there may be a larger environment than has been recognized which must be taken into account in looking for elements contributing to maladjustment and neuroses. Dangerous as it would be to endow these hypotheses with more than a status of possibility, it might be equally hazardous to neglect them in the study of the underlying causes of mental disorders.

In considering the possible bearing of the parapsychology research upon psychiatry, the work in psychokinesis or the direct influence of the mind upon matter should also be mentioned. The findings on psychokinesis or PK are a natural derivative of the ESP researches. Logically, if a psychophysical action occurs which enables a subject to identify a concealed object, we should expect as a reaction that the object is in some way affected. By means of a delicate process, such as the random fall of dice, the influence of the PK effect of the subject upon the object has been sufficiently well and carefully demonstrated that we now have this other end of the psychophysical interaction to deal with. We consider it another aspect of psi phenomena—the direct action of the subject upon the object. We do not know as yet how extensive this capacity may be or how it operates, but in that we are but little more ignorant than we are concerning the more familiar functions of personality. There is not enough time to summarize the extensive experimental work that has been done to establish the PK effect,[1] but the conclusion rests upon a firm foundation of experimental research to which a number of independent investigators have contributed. One of the best and most recent of these confirmations is the recent work of Dr. Thouless, soon to appear in print.

Once one accepts the PK principle, many applications of hypothetical character come to mind. Some of them are of peculiar interest to the psychiatrist. In PK we have a possible explanation for some of the hitherto unexplainable effects reported from psychosomatic medicine. Again, I am speaking only of possibilities. Just what the explanation is when a wart disappears or a blister is produced psychogenetically has yet to be discovered. It may be that PK is not involved in any of these effects, but it must be recognized as a possible explanation with nothing very plausible as an alternative.

It is still harder to reject the PK hypothesis in the cases of claims of removal of warts and other growths from animals by charms—if indeed such claims have any basis in fact.

If accentuated research interest can be directed to this area, we may be able to promote study of some of the challenging physiological problems which have been left too long on the shelf because of their unconventional character. So far as I know, Gorer's [15] report of timing a West African Negro's submersion under clear water for forty-five minutes stands uninvestigated by any appropriate branch of science. The reports of suspended animation by the fakirs of India may be exaggeration or malobservation, but if they are, that too is something we should know. Many reports of unexplainable biological effects are recorded which have never been taken seriously. There are cases of the unaccountable development of lactation in a dog when another bitch with which it played had puppies. Even the psychogenic production of lactation in human beings is reported by anthropologists. Dermatologists insist that the sudden greying of hair is impossible, but there are actual cases of its occurrence. There is no lack of serious testimony to these unorthodox types of physiological phenomena, and so long as we are dealing with psychological unknowns it would be poor science on our part to fail to collect all possible types of application, while at the same time reserving judgment as to their validity.

It is not unlikely that the psi functions of ESP and PK are basically related to the organizing system of the individual that presumably has to do with health and disease and with the processes of growth and adaptation and inheritance. The rounding up of the exceptional manifestations of biological character that suggest parapsychological causation may conceivably furnish new hypotheses for the study of the fundamental directive processes of the living organism. The mere possibility should suffice to justify such a survey.

Another area of common interest, though also unfortunately of common ignorance, is that of the important relation between thought and the brain. Most psychiatrists, like most psychologists have, I believe, settled down to the working assumption of a psychosomatic unity of some unknown sort. Since there is a great deal more known about the physiological end of this unity axis, the majority of psychiatrists have gradually drifted around to a relatively physicalistic approach in dealing with the mind-body system of human person-

[1]For a general account see my book "The Reach of the Mind" [28] and for most of the original reports, *The Journal of Parapsychology*, since 1943.

ality. Everyone agrees, of course, that no one really knows how far physics goes in explaining the patient's mental life. But since it does go a long way toward the explanation of neural action, the drift has been steadily toward a mechanomorphic conception of the individual and a discouragement to the search for anything nonphysical in human nature.

This need for unity is understandable. Our conception of causation requires that some kind of unifying explanation be found to account for all the interacting elements in nature. But the more pressing question for the sciences dealing with man is that of how much diversity there is within the unitary system of the individual. It is a problem of determining what order of complexity man has in his nature, as a first step in ascertaining his fundamental nature and organization.

If there is nothing in personality beyond physical operation, then psychiatry, like all the other sciences dealing with human beings and human relations, becomes identifiable as a branch of physics. If a brain-centred, physicalistic view of man is correct, then the psychologist is a physicist and the psychiatrist is obviously an engineer. He cannot regard himself as dealing with a purposively intelligent, volitionally free, self-directing person. This conception would have to be discarded as just another superstitious hangover from our religious past, as would also any psychotherapy dependent on the volitional or purposive effort of the patient. One does not look for volitional freedom or purpose in a physical system, no matter how ingeniously elaborate it is.

If, on the other hand, we find there *is* something nonphysical in human personality, then, of course, we have an order of reality with which to deal that science has hitherto never really taken seriously. Such a step would be of course a radical and revolutionary one, and could not be taken without the most solid sort of evidence to back it. If it should be found that man has a certain amount of far-reaching diversity in his nature, if there is a differentiation of function within the personality, even though this cannot conceivably be an absolute and ultimate distinction, it should allow for the interplay of different systems of lawfulness, providing a structure that permits one part to be free or independent from the other to a certain extent. *Without* such relative differentiation there would be nothing that could be free from anything else and freedom would have no meaning. Such a conception, of course, still leaves many questions unanswered, but it answers one question of fundamental importance in dealing with human beings. How is freedom of choice possible? At any rate, no one has found any other way to make reasonable this theory of himself which man has rigidly held in all ages and climes, namely, his belief in his volitional freedom?

We have, then, the two views of the place of personality in nature, the brain-centred or physicalistic view and the mind-centred or the nonphysicalist conception. Is it not reasonable to say that upon which of these two views is correct will eventually depend not only the future conception and practice of psychiatry, but of every other science of human nature as well?

But is there any longer really a question of choice in the matter? Extrasensory perception does not appear to follow any physical criteria to which it has been subjected. The advantage of this mental process is that it can be set up against the time-space framework and its relationship to these criteria of the physical world made a matter of actual test and measurement. Extrasensory perception has succeeded over distances as great as four thousand miles. Comparative experiments at shorter distances have shown quite as good ESP results at one hundred yards, for example, as obtained at one yard distance. Tests made at a distance of two hundred miles and two feet showed no significant difference in results. The work on precognition or ESP of the future, is technical and elaborate. It has not advanced to an extent comparable to the conquest of distance, but the mere establishment of precognition of any kind as a genuine occurrence takes us out of the realm of physical concepts for an explanation of the phenomenon concerned. While there is, no doubt, a great deal more to be done, especially in trying greater lengths of time in further precognition experiments, those who have followed the researches of ESP in time and space have rather unanimously been forced to concede that there seems to be no relationship found or even suggested within the range examined.

It must be conceded that we do not yet have an explanation for these phenomena. But for what fundamental aspect of mental life *do* we have an explanation? Perhaps the only point parapsychology need claim to have made is that we are dealing with a subdivision of functions of human personality, some of which defy explanation in terms of those properties and principles that have so effectively explained matter. In an area in which there has been only speculation and blind faith in the past, these findings come as a fresh and compelling orientation. They have started our thinking very definitely along lines unhampered by mechanistic dogma. No one can say yet where this evidence of the nonphysical nature of these mental operations will eventually lead, but it should at least liberate the sciences of man from the impasse into which three centuries of over-emphasis on matter have led them.

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Dr. R. H. Thouless, Reader in Educational Psychology, University of Cambridge :

Contrary perhaps to general expectation my brief remarks will not be of a critical nature. When Professor Rhine and his colleagues published, in 1940, their book, "Extrasensory Perception after Sixty Years", they did me the honour of listing me as one of the six leading critics of the extrasensory experimental work. But that is a condition of things long past. About the odd facts of parapsychology of which Professor Rhine has been talking, I can only say that I have got similar results myself and can, from my own experience, confirm their findings not only in extrasensory perception but also in precognition and psychokinesis. I should like briefly to refer to what I think is the main importance of the facts of parapsychology to psychological theory and, therefore, indirectly to the practice of psychiatry. For the last century we have got into a way of talking about mental facts which gets rid of the old-fashioned view that these are activities of a psyche or soul. Mental facts are regarded as aspects of neural processes. If this were an adequate theory, it would seem that the facts reported in parapsychological research would not take place. The fact that they do take place suggests that we may have to reconsider our rejection of the soul. If so, the matter is important to psychiatry as well as to general psychology. It is reasonable to suppose that we shall best succeed in curing the mentally sick if we work on a true theory of the nature of mind.

Section of Ophthalmology

President—M. L. Hine, M.D., F.R.C.S.

[*March* 10, 1950]

Meeting Held at the Moorfields Branch of Moorfields, Westminster, and Central Eye Hospital

Exophthalmos

Dr. F. A. Elliott showed five cases of exophthalmos illustrating the difficulties in diagnosis and the dangers of incorrect treatment:

I.—Granuloma of right orbit in a man of 36. Five months' history of diplopia followed by increasing proptosis. There was a marked sense of resistance on attempting to push the eye back into the orbit. Diagnosis confirmed by exploration.

II.—Exophthalmic ophthalmoplegia in a woman of 37. In this case bilateral proptosis appeared four months previously, diplopia occurring eventually. The left eye receded after a few weeks, but the right-sided proptosis and the diplopia persisted. No evidence of thyrotoxicosis and no bruit.

III.—Exophthalmic ophthalmoplegia in a woman of 35 with diplopia. Three months' history. At the onset there were signs of mild thyrotoxicosis, which disappeared on Lugol's iodine, and did not recur, although the proptosis is severe and closure of the lids difficult.

IV.—Exophthalmic ophthalmoplegia in a woman of 30. In this case there were no thyrotoxic features, either clinically or by laboratory tests, but increasing disfigurement caused symptoms of an anxiety state which were mistaken for thyrotoxicosis. Thiouracil and subsequent partial thyroidectomy caused a mild myxœdema, increasing anxiety, and aggravation of the exophthalmos. Papillœdema and a reduction of visual acuity necessitated decompression of both orbits.

V.—Unilateral proptosis due to carotico-cavernous fistula in a woman of 28. The proptosis was not accompanied by visible pulsation of the eye, or by a palpable thrill. Retinal veins were distended and there was a marked intracranial bruit with systolic accentuation. There was a curious absence of any œdema of the eyelids.

Dr. Elliott also showed a case of **Unusual Ocular Movements** in a girl of 18. Normal in every other respect, she could voluntarily roll both eyes synchronously in a clockwise direction at the rate of 4 cycles per second. The upper eyelids moved up and down in time with the eyeballs. She reported that—as in voluntary nystagmus and occupational nystagmus—external objects appeared to move when she was performing this feat.

Mr. John Foster said that, in the early days of the silent cinema, when a great deal of the humour depended upon what is now known on the stage as "mugging", there was one character who used to appear in the guise of a crazy prospector or airman, who was quite obviously able to induce nystagmus of a rapid and rotary type at will.

He himself had wondered from time to time whether it was possible to re-induce the signs of miner's nystagmus when once one had suffered from it and had ceased to suffer from the nervous effects. On one occasion a miner was examined by a colleague, whose examinations were always extremely prolonged and careful for this disease, and showed no signs of the disease whatever. Within two days he was seen by the speaker and by another colleague and had an apparently spontaneous miner's nystagmus in daylight and at the horizontal level.

Such a case must make one wonder as to whether auto-induction of the signs of the disease is possible.

With regard to the differential diagnosis of the various forms of exophthalmos, there was no doubt that the orbital resistance as measured by the orbitonometer of Copper provided a most useful additional method of diagnosis in deciding whether the patient had Graves' disease, a tumour of the angiomatous type or malignant exophthalmos of the thyrotrophic type.

Mr. A. McKie Reid said that some years ago he came across a girl who was able to produce a most remarkable rotatory nystagmus. As she stared, she was able, voluntarily, to start a rotation of her eyes at a rate of about three cycles to the second; and could stop it just as quickly. He also recalled the case of a miner in North Wales some years ago who was not only getting full compensation for miner's nystagmus but also drawing a blind pension; and who could produce, at will, an oscillation typical of that of miner's nystagmus. During the same period he was to be seen riding a bicycle night after night outside the town. Yet he had convinced ophthalmic surgeons on both sides—both for the employers and for the Miners' Federation—that he had a disabling nystagmus.

Corneal Graft

Cases treated by corneal grafting were demonstrated by **Messrs. A. Lister** (3 cases, 1 bilateral); **A. S. Philps** (3 patients, 1 bilateral); **Harold Ridley** (4 cases); **D. P. Greaves** (bilateral); **E. F. King** (2 cases); **B. W. Rycroft** (3 cases).

Speaking of the selection of cases for operation, Mr. Lister referred to the three prognostic groups illustrated by his cases; good in the case with familial corneal dystrophy; doubtful as shown by a case of interstitial keratitis with one successful and one unsuccessful graft; and hopeless in one with a staphyloma.

Mr. Philps spoke of the safety and excellent results of the lamellar grafting and Mr. Harold Ridley of the value of using trephines of the same size for both donor and recipient eyes to render the cornea immediately watertight thereby promoting rapid reformation of the anterior chamber and avoiding anterior synechiæ and glaucoma.

In Dr. Greaves' case of bilateral graft—using cadaver material for one, and fresh for the other—results were equally satisfactory, in spite of a corneal abscess in the cadaver graft, which resolved with chemotherapy. One of Mr. Rycroft's cases illustrated the complication of keratitis in the recipient eye invading the graft. He spoke well of lamellar grafts.

Mr. Tudor Thomas said that some beautiful results had been shown. He believed that with a shelving margin to the graft there was less danger of anterior synechiæ taking place. He agreed with Mr. Philps who said that the lamellar graft was the most suitable treatment in certain cases. They had a choice now of the penetrating graft, the lamellar graft, beta-ray therapy and keratectomy; quite a variety of treatments. He felt that, particularly in carefully chosen monocular cases the lamellar graft was a very useful form of approach.

Preziosi's Operation

Mr. J. D. Magor Cardell, *in absentia*: Preziosi described his operation in 1924, *Brit. J. Ophthal.*, **8**, 414. Since then various modifications have been made which have resulted in a simple operation applicable to all types of glaucoma.

It has certain advantages which include the brief time taken to perform the operation, the only instrument that enters the eye is red-hot and therefore quite sterile, the A.C. is reformed in twelve to twenty-four hours, the patient is usually up on the second or third day, and out of hospital on the seventh. The main disadvantage is that it is sometimes painful and so an injection into Tenon's capsule is now given.

So far, it has been more effective than other operations on hæmorrhagic glaucoma in making the patient comfortable and keeping the eye in the head.

The value of an operation may be assessed by those cases that do not respond satisfactorily. Out of 35 cases there were 10 of this type. 3 required further operation, 3 were easily controlled by miotics, in 3 the post-operative rise of tension was evanescent and in 1 the flap had to be mobilized. Four cases illustrative of various types of glaucoma on which the operation had been performed were shown.

Mr. Humphrey Neame said that he had nothing to add to the description which Mr. Cardell had given. There was no doubt that Preziosi's was a simple operation to perform. Personally he did not use atropine in the operation. He made the point, before operation, of getting the pupil as small as possible and keeping it small with eserine afterwards. In one case in which he did not get a very small pupil beforehand the iris came up and prolapsed. Peripheral iridectomy had to be done. He personally preferred to use eserine before and after until the eye had quietened down.

Mr. A. Lister said that what had impressed him in the few cases of Preziosi's operation which he had done was the comparative quietness afterwards. The eye did not react so much after this operation as it did after the trephine.

Detachment of Retina in Aphakic Eyes

Mr. C. Dee Shapland showed 4 cases of successful reposition by diathermy, 1 following needling of lamellar cataract, 2 following extracapsular extraction and 1 after a successful couching of a cataractous subluxated lens. This last case was shown at the joint clinical meeting of the O.S.U.K. with the Section of Ophthalmology of the Royal Society of Medicine on May 31, 1946 (*Trans. ophthal. Soc. U.K.*, 66, 376). The visual acuity of this eye remained good until 20.11.48, when the retina detached. Operated upon on 29.11.48, surface diathermy and katholysis punctures, the retina has remained in place ever since, with central vision 6/24 with aphakic correction.

Scleral Resection

Mr. A. S. Philps said that the technique of this operation had already been described, and he wanted only to mention results. He showed a list of cases done in 1948 and the early part of 1949. They included 4 with aphakia, 4 with emmetropia, and 4 with myopia. The 4 with

aphakia all went back; of the myopes only 2 went back, and of the emmetropes 3 went back. Of the 6 patients shown by him at this meeting 2 were women who had had the operation as first choice two weeks ago, and apparently it had been successful.

Mr. Philps showed charts and drawings of the cases, and added that it did seem that in an aphakic detachment with a lot of capsule in which the periphery of the retina was quite obscured so that no hole could be found, it was possible that scleral resection might be the operation of choice rather than a blind diathermy which produced a severe reaction. The reaction produced by it was less than with diathermy. He hoped that ophthalmic surgeons would try it because it offered a prospect for eyes which otherwise undoubtedly would be lost.

Mr. A. Lister showed 3 scleral resections which, he said, were not representative of his results, because they were all successful. He had done 17 scleral resections, and in 6 of these the retina went back. 5 of the 17 were myopes (1 successful); 3 were degenerative (2 successful); 1 was a ten-year-old traumatic dialysis (successful), and 8 were cases of aphakia (2 successful). In a number of cases classed as failures there had been some apparent improvement after operation. The most important aspect of the operation was that a wide field was covered and a gentle reaction obtained. In a case where the retina was torn or was thin or atrophic, scleral resection was more likely to be successful than diathermy owing to the nature of the reaction induced. He applied potash (3%) to the exposed choroid as the operation proceeded so that it included part of Guist's technique—but was easier.

Mr. Philps, in reply to questions, said that he had never perforated the choroid. During the resection the choroid sometimes tended to bulge, and when it did so a cautery puncture was made further back in the eye, away from the wound, to let out some subretinal fluid, after which the choroid did not bulge any more.

He had not used diathermy very much, not because he had any objection to it, but because he had wanted to try one thing at a time. It was always the aim to get resection over the hole or holes, and possibly the retina over the holes was collapsed. Again, with scleral resection there was a mild reaction over a wide area of tissue such as could not be produced with diathermy without destroying the eye.

Intra-ocular Growths Treated by Irradiation or Diathermy

Mr. H. B. Stallard demonstrated 2 cases of **Malignant Melanoma of the Choroid** successfully treated by a radium plaque sutured to the sclera.

Mr. Harold Ridley brought forward 2 cases to illustrate different methods of treating **Retinoblastoma.**

In the first case, aged 2¼ years, there was a single tumour consisting of a column of cells growing from the retina several millimetres into the vitreous. This case he thought best treated by radon seeds, the radiation of which spread to the apex of the tumour and did not affect only its base. Two applications were required before this retinoblastoma was completely destroyed.

In the second case, aged 3 years, there were five or six small flat plaques of retinoblastoma each about 1–2 mm. in diameter in various regions of the retinal periphery. To have treated these with radiotherapy would have entailed encircling the eye with radon seeds with unnecessary risk of damage to the growing lens. These tumours could, however, be destroyed by the application of surface diathermy to the overlying sclera, the current employed being 90 ma. for eight seconds. The only difficulty was to decide whether the white area seen after treatment was diathermy coagulation or untreated tumour. He did five applications the first time, and three weeks later found one area which had not been completely treated and a new tumour which had since appeared. All six tumours had now been destroyed and the child saw quite well and had apparently good central vision.

Polyarteritis Nodosa

Mr. E. F. King said that this patient was a tragic case. He was a man of 23 years of age who was admitted to hospital some months ago because of thrombosis in both eyes of the superior temporal branches of the central retinal veins. A bilateral uveitis of great severity, with secondary glaucoma, rapidly developed and to-day he is almost blind. During this period he had had a low-grade toxæmia and, from time to time, small inflammatory nodules had appeared beneath the skin, chiefly on the neck and legs. A biopsy of these nodules suggested the diagnosis of polyarteritis nodosa. During the last war this man had an ear infection which was treated by sulphonamides and penicillin and it was suggested that his present condition might be the result of an allergic sensitivity to one or both of these.

Optic Atrophy in Methyl Alcohol Poisoning

Mr. E. F. King said that this patient alleged that he drank methylated spirit, but it was not quite clear if this was the cause of his optic atrophy.

The atrophy in both eyes was extreme and all the retinal arteries were markedly narrowed.

This patient's blood pressure was in the region of 260/180 and it was difficult to be sure if he had had bilateral embolism of the central retinal arteries, intense spasm of the arteries due to methylated spirit, or was a case of true toxic amblyopia.

Cutler's Implants

Mr. J. R. Hudson demonstrated two cases. The technique employed for the introduction of the Cutler's implants is fully described in the *British Journal of Ophthalmology*, 1950, **34**, 251.

Mr. A. Lister said that the case he showed was one of delayed implant. The sunken socket and unsightly appearance four years after the loss of the eye made it seem worth while to put an implant in, and this proved easier than he had expected. The muscles were identified under local anæsthesia by making the patient look in different directions and a stitch was put through each dimple so caused. A block of tissue was removed, under general anæsthesia, from between them and the implant was then put in and fixed in the usual way.

One point that implants had brought home to him was that it was quite unnecessary to take out an artificial eye and wash it from time to time. The eye remained perfectly clean, probably cleaner, if left alone.

Mr. P. McG. Moffatt mentioned the case of a patient who had never had his artificial eye taken out for seven years.

Other Members supported the point that the eye need not be taken out, and that no inflammation or other trouble resulted.

Diabetic Retinopathy

Two instances of diabetic retinopathy in young people were shown:

Patient aged 34 by **Dr. G. D. Elphick**; patient aged 21 by **Dr. John Lister** for **Mr. H. E. Hobbs.** Dr. Lister described the finding in the latter case of rt. bundle branch block which was at first thought to be evidence of a myocardial vascular lesion, attributable to the diabetes. Cardiac catheterization, however, showed the defect to be congenital and associated with an atrioseptal defect.

The age of the patient, 21, would have been of more interest some time ago than it was to-day, because there was now evidence that diabetes with retinopathy did occur in the younger age-groups. In a review of the incidence of retinopathy in diabetics, Wagener and Wilder in 1921 found that it was 8·3%; in 1934 it had risen to 17·7%, and in 1945 to 30·6%. They did not give a very clear reason why it was rising but presumably it was due to the longer life of diabetics. In the present series Wagener said that he had 12·8% of retinopathies occurring in patients under 40 and 8·3% in patients under 30, whereas in his first series, in 1921, there was no case of retinopathy under the age of 40.

These investigators also gave figures indicating the importance of the duration of the diabetes. It was still a matter of great doubt as to the ætiology of the retinopathy. Most people seemed to agree that diabetic retinopathy was a specific lesion, and even glycosuria did not seem to be essential, although an abnormal glucose tolerance curve was always present.

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The following cases were also shown:

Congenital Pigmentation.—Dr. W. M. DE C. BOXILL.
Scleral Resection for Retinal Detachment.—Mr. A. G. CROSS.
(1) Traumatic Ptosis (Everbusch) with Cartilage Orbital Implant. (2) Canaliculo-Rhinostomy. (3) Cantho-Rhinostomy (2 Cases).—Mr. B. W. RYCROFT.
Neurofibromatosis.—Mr. E. F. KING.
Cutler's Implants.—Dr. L. G. FISON.
Krukenberg's Spindles (2 Cases).—Mr. J. R. HUDSON.
Child with Macular Lesions (for Diagnosis).—Mr. J. R. HUDSON for Mr. A. J. B. GOLDSMITH.
Aqueous Veins (Three Typical Examples).—Mr. S. J. H. MILLER.
Diplopia Operatively Corrected.—Mr. H. E. HOBBS (2 Cases); Mr. T. KEITH LYLE (2 Cases).
(1) Congenital Pigmentation of the Fundus. (2) Pigment Adjacent to Disc and ? Choroidal Mole. (3) Retrolental Fibroplasia and Congenital Retinal Fold.—Mr. A. G. CROSS.
Retinal Atrophy.—Dr. G. D. ELPHICK.
Diabetic Retinopathy.—Dr. N. PINES.
Choroido-Retinitis.—Dr. H. L. BACKHOUSE (introduced by Mr. FRANK W. LAW).
Iridoschisis.—Mr. P. McG. MOFFATT (*see* December 1950 *Proceedings*, Sect. Ophthal.).

Section of Orthopædics

President—NORMAN CAPENER, F.R.C.S.

[*February* 7, 1950]

Syme's Amputation Sixty-five Years Ago.—W. D. COLTART, F.R.C.S.

Mr. F. S., aged 73.

Sixty-five years ago Mr. Whittaker performed a Syme's amputation at St. Bartholomew's Hospital. The patient thinks that the amputation was performed for a tuberculous lesion. The stump has remained free from trouble and he has been a lorry driver for forty years.

Osteochondritis of the Patella.—B. H. BROCK, M.B. (for St. J. D. BUXTON, F.R.C.S.).

Boy, aged 7 years.

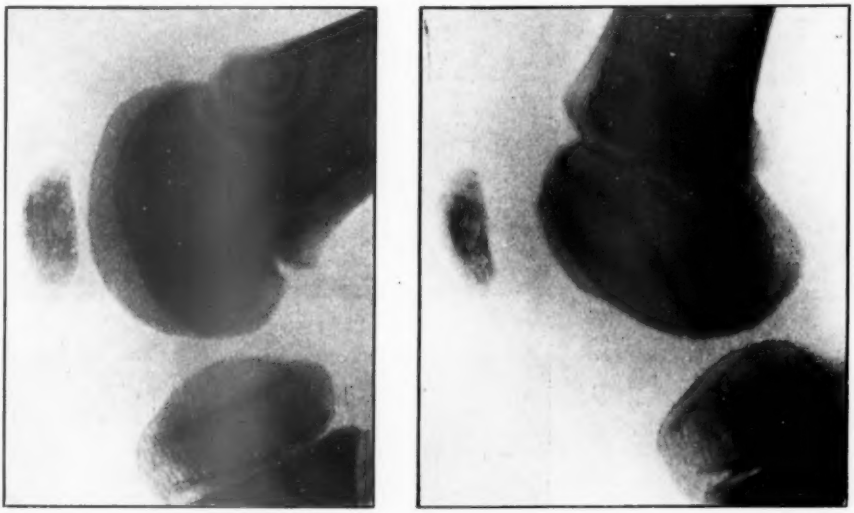
First seen two weeks ago, complaining of swelling of the left knee and occasional "giving way" for four months.

No history of trauma or infection. Tonsils had been removed in December because of persistent sore throats. This had had no effect on the condition of the knee.

On examination.—No abnormal signs in the knee other than a moderate effusion. X-rays show stippling of left patella, very suggestive of osteochondritis.

B.S.R. normal. Tuberculin patch test negative.

Fluid aspirated from knee sterile; no acid-fast bacilli.



R. L.

FIG. 1.—Osteochondritis of the patella. Radiograph showing irregular density of the left patella compared with the normal.

Mr. C. Hope Carlton spoke of a similar case in his practice in which a schoolboy had had to give up football on account of pain in the patella. Rest in bed gave only temporary relief. The external lower quadrant of the patella was mottled and extra-articular excision of this mottled quadrant was carried out. All pain had since disappeared and football had been resumed.

The President said he thought this was a case of low-grade infective arthritis with a vascular patella. Perhaps Mr. Brock would report the case again in six months' time.

POSTSCRIPT (8.9.50).—This boy was treated in a walking plaster followed by a backsplint for two months, after which time the X-ray changes in the patella became less apparent and effusion of the knee disappeared.

After six weeks' physical treatment he had no symptoms, and the patella was virtually normal. It seems likely that the diagnosis of osteochondritis was in error and that the opinion of the President was correct.—B. H. B.

Von Recklinghausen's Neurofibromatosis with Bone Changes.—J. ADDISON, F.R.C.S. (for J. S. BATCHELOR, F.R.C.S.).

Miss P. H., aged 40.

Pain and stiffness right groin and upper thigh for six months.

Treated at Guy's Hospital when an adolescent for deformity of spine. Given remedial exercises.



FIG. 1.



FIG 2.

On examination.—Gross kyphoscoliosis of thoracic spine. Numerous skin tumours and café-au-lait patches (Fig. 1). Right hip movements moderately restricted. Right leg ¾ in. lengthening.

Radiographs show bone changes in right femur, right side of pelvis, spine and ribs (Figs. 2 and 3).



FIG. 3.—Showing changes in right side of pelvis, with narrowing and elongation of femoral neck and ectopic bone formation about lesser trochanter.

Mr. R. H. Metcalfe said that he had a woman patient who complained of pain in the right shin. She was suffering from generalized neurofibromatosis of long standing and on examination there was gross enlargement and forward bowing of the right tibia with 2 in. lengthening. He asked the advice of Sir Thomas Fairbank who stated that a similar case had been published by Willis C. Campbell (*Surg. Gynec. Obstet.*, 1923, **36**, 669), and he, himself, had operated on such a case, shortened the bone and got satisfactory union.

Mr. Metcalfe said that he had shortened the bone and his patient was now walking in plaster, free from pain.

Mr. L. S. Michaelis described a condition of kyphosis seen in two brothers. One of the boys had signs of compression of the cord, and laminectomy was considered, but it was decided instead to put him in extension. As a result of this treatment all signs of compression of the cord disappeared and had not recurred. The fact that two brothers were affected in an exactly similar manner showed that this was a congenital affliction. Both the skin and the bone systems were congenitally affected in some way.

The President said that members probably realized that such forms of scoliosis could occur without dermal neurofibromatosis in people, generally of dark complexion, with pigmented areas on the skin. They were quite characteristic individuals. The radiographic appearances of the femoral neck in the present case called to mind Murk Jansen's illustration dealing with "Dissociation of Bone Growth" in the Robert Jones Birthday Volume. Jansen would probably have regarded this as an example of progressive retardation of cell division in the growth disc.

Congenital Absence of Biceps and Malformation of Right Elbow.—R. C. F. CATTERALL, F.R.C.S.

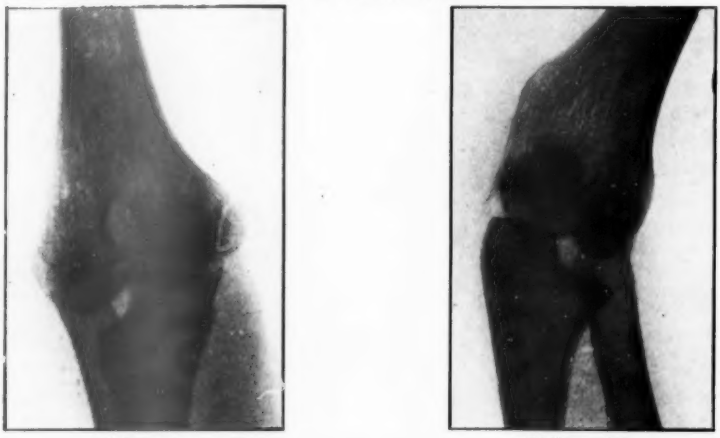
W. J., male, aged 13.

First attended hospital complaining of pain in the knees which was found to be due to Schlatter's disease; has now recovered. It was noticed that he had congenital absence of biceps, for which no treatment had been undertaken although he was attending a special school.

Admitted three months later, following a Monteggia type of fracture of right arm which was treated by open reduction in May 1949. The head of the right radius was grossly deformed, but the tendon of the biceps was present.

The fracture has united with some malunion and flexion is limited (Fig. 1).

The patient was presented for advice on further treatment.



A.P. view Oblique view

FIG. 1.—Right elbow, showing residual deformity after fracture. The joint movement is locked by the deformed head of the radius.

Mr. Catterall proposed that after excision of the head of the right radius to overcome the bony blocking of flexion, Clark's operation of partial pectoralis transplant should be carried out.

Mr. E. J. Nangle said that Clark's operation had been tried in one case. In the first place, it was difficult to dissect the pectoral muscle, and when it was done it was of very little use. He strongly advised not to try the operation in this type of case as the muscle was abnormal.

The President said that he regarded the case as one of segmental dysplasia of neurogenic origin rather than a generalized condition. He was doubtful about Clark's operation in a patient who did not appear to be very co-operative.

The possibility of an elbow-cage powered by a pectoral muscle motor was mentioned by Mr. Catterall, but no support for this method was forthcoming.

POSTSCRIPT (30.9.50).—The head of the radius was excised but no further movement was obtained owing to the shortened triceps. Further surgical treatment has therefore been abandoned. R. C. F. C.

Bilateral Congenital Dislocation of the Patella.—IAN MACNAB, F.R.C.S. (for K. I. NISSEN, F.R.C.S.).

A. W. was first seen at the Royal National Orthopædic Hospital when she was 4. Her parents stated that she was never sure of herself when walking and that without provocation she would fall over about five or six times a day.

On examination it was found that both patellæ were dislocated laterally. She was able to extend her right knee fully by kicking it out and locking it in extension but she was unable to hold her knee in any position between full extension and 90 degrees flexion. Extension in the left knee was 85 degrees short of full movement. X-rays confirmed the clinical diagnosis of congenital dislocation of the patellæ of both knees, one of which is seen in Fig. 1.



FIG. 1.



FIG. 2.



FIG. 3.

It was held that surgical intervention was justified because the child fell over so frequently without warning that it was dangerous to let her go out by herself. It was felt that it was necessary to restore the mechanical efficiency of the knee by transplanting the patellar tendon medially and to combine this procedure with excision of the patella. Patellectomy was considered to be advisable for two reasons: firstly because the patella is so frequently malformed and misshapen in these cases, and secondly because transplantation of the patella tendon in one so young carries with it the risk that its new attachment will migrate distally with continued growth. If the patella is not excised this may lead to incongruity of the patello-femoral facets and disability later. The left knee was operated on first by Mr. K. I. Nissen in 1947 using the procedure described above, and two years later a similar operation was performed on the right knee. After the second operation it was noticed that the quadriceps tendon of her left knee dislocated medially on full flexion. It was decided that the patellar ligament had been transplanted too far medially. In October last, 1949, the original operation was revised and the insertion of the patellar ligament placed ½ in. laterally. The child now has full return of function to both knees (Figs. 2 and 3).

Section of Pædiatrics

President—W. W. Payne, M.B., M.R.C.P.

[*March* 24, 1950]

DISCUSSION: GROWTH AND DEVELOPMENT STANDARDS AND THEIR CLINICAL APPLICATION

Dr. D. MacCarthy: Recent advances in anthropometry and their application to clinical work in children should be of interest to pædiatricians. It is in the sphere of the health of the school child and the detection of the ailing child at school that standards of growth and development have their most important application, whereas it is with the pre-school child or the sick child that the majority of pædiatricians have to deal.

The essential difference in the two circumstances is the fact that we are usually seeing the child for the first time and have only one set of data, whereas the school medical officer has data extending over a period of time and is able to take a longitudinal view of the child's development. Take the example of the child who is brought to us because he appears to be too thin, does not seem to grow, will not eat and looks "run down"—one of the commonest problems in pædiatrics. The clinical examination includes an estimate of the child's state of nutrition and physical development. This estimate implies a reference to some standard, whether it be tables of measurements or only the physician's memory of other healthy children of the same age. One doctor calculates that the age of the child plus three, multiplied by five gives approximately the expected weight. Another turns the pages of a much-thumbed pharmacopœia to find a table of average heights and weights for age (usually Holt's). Another looks up to the wall where hangs a scroll, now turning somewhat yellow, with a similar set of figures. Another refers to tables which he has culled from the literature (such as the Menzies Report 1938 or Gore and Palmer's figures (1949) for children under 5). Yet another proceeds to make further measurements and may even produce a pair of calipers and measure the width of the child, after which he proceeds to look up the answer, using several tables (probably American) giving percentiles or standard deviations. He finds that 1 in 25 healthy children or perhaps only 1 in 100 will fit into those measurements and he carefully weighs this fact with the rest of his clinical findings.

This assessment may be the starting point of various courses of action; for instance, more elaborate clinical investigations are undertaken, the child may be sent to a convalescent home or even to an Open Air School and not infrequently tonsillectomy is recommended.

The fallacy of clinical assessment of state of nutrition is now well known. Huws Jones in 1938 conducted a trial in which five school medical officers assessed the nutritional status of a large number of school children. The doctors were in unanimous agreement in their judgment on only 22% of the boys.

Suppose that in the case of the child we are examining we confirm our clinical impression that he is abnormally short or thin by reference to Holt's charts for height, width and weight; suppose also that ordinary investigations do not point to any organic disease; what do we know or what would we like to know about other factors that may influence the child's growth?

(1) *General trends.*—The stature of children as a whole has increased in the last three decades; Campbell and Weir (1948) estimated, using Tuxford's Index, that London school children in 1938 were taller at all ages (and also 7·5% heavier for their increased heights) than the children of 1912. These tendencies make us uneasy about the validity of any standards we may use—even if they are only 10 years old.

(2) *Environment.*—The stimulus of the cold conditions in an open-air school or the change of environment and diet of a convalescent home, seems to boost the powers of growth and produce a sudden increase in height and weight. This rate of improvement cannot of course be maintained for long. In convalescent homes where they take careful measurements the staff are aware of this period of maximum benefit and may take it into account in determining the child's length of stay. A marked response of this kind is also a confirmation that the child's former state was subnormal.

(3) *Infections.*—Certainly the weight lost in acute infections is rapidly regained (though whooping cough is an exception) and it is doubtful whether even repeated acute infections appreciably alter the height and weight attained by a child from year to year.

(4) *Birth weight* (5) *Size of parents* (6) *Seasonal fluctuations.* (*These subjects were further discussed by Dr. E. R. Bransby, Dr. C. Asher and Dr. J. W. B. Douglas.*)

Standards of reference are also required by the clinician in following up his patients. All too often the weight is taken as the sole guide, whereas increase in height is probably a truer index of sound nutrition. This is particularly true in cœliac disease. (*An example was given.*)

In their attitude towards the evidence of anthropometry clinicians are divided into two classes. Those with much (and usually local) experience, who would always prefer to trust their clinical sense to sift out the child who is not growing as he ought (and they will usually be right); and those with moderate or little experience who feel that not only is an additional check on their assessment needed, but as in any other study of nature, constant reference to a reliable definition of the normal is the quickest way of learning to detect the abnormal. This might be called the Procrustean school, for Procrustes, the Father of Anthropometry (unfortunately an obsessional type with strongly sadistic tendencies) was after all working on these lines. If he had had a wider conception of the normal; if he had had a series of beds instead of one and had kept records, the story would have been very different and the science of anthropometry would have started then and there!

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Dr. J. M. Tanner: (*Summary*) (1) In setting up standards for the growth of healthy children we may use distance, velocity or acceleration data. That is to say, we may inquire whether a given child is of normal stature at, say, age 6; whether his increment in stature from age 5 to 6 was normal; or whether his deceleration over a similar period was normal. Probably standards of *increment* will be the most generally useful, at least in circumstances where two measurements of the same child are available, as in the school health service. Since the universal practice up to the present has been to use distance standards, no incremental ones are immediately available, despite the raw data on standardizing series having been accumulated. The point has been examined in some detail elsewhere, together with a general account of the reporting of growth data [1].

(2) A precise understanding must be arrived at as to what we mean by, for example, "abnormal in height increment from age 5 to 6". The definition of abnormal must be an arbitrary one and, at least for routine screening purposes, refer to the likelihood of the given child having been drawn from the same population of children as the standardizing data are drawn from. The confidence level for rejecting the hypothesis that he does so belong (i.e. is not abnormal) should vary according to the further steps to be taken if the decision of "abnormal" is made. If the child is then merely sent for further specialist examination, the confidence level could be quite low, say 1 in 10, allowing 10% of normals to be treated this way also, while if the next step is operation, the level should be high, say 1 in 250 or more.

(3) The test of normality in one of the two major sets of standards available [2] is couched as the given child's deviation from the mean figure compared to a percentile distribution of the population; of the other [3], compared to a standard deviation unit of the population. The choice here should depend on the distribution of the given bodily measurement in the healthy population. If the distribution is normal, standard deviations are greatly to be preferred, since then the sampling error of the $1{\cdot}96\sigma$ and $1{\cdot}65\sigma$ levels is considerably less than that of the upper 97½th and 95th percentile points. For skewed distributions, however, the standard deviation test, particularly if one-sided, is somewhat objectionable. The most efficient course would be to provide transformations of skewed data to get them to the normal distribution.

(4) The standards mentioned in paragraph 3 are essentially distance standards, whereon increment is gauged by eye by plotting the given child's distance achieved twice or more and seeing if the child's curve runs parallel to the standard distance curves. This is an unnecessarily crude way of evaluating the child's increment and provides no actual test of the hypothesis mentioned in paragraph 2. A better arrangement would seem to be to print sheets where both distance and increment standard curves were given, each with the limits for varying confidence intervals for "normality". The child's position should then be simultaneously plotted in both.

(5) The efficiency of standards can be greatly increased by the use of regression equations, allowing, for example, for height and hip width in standards for weight. The terms in the equation can relate either to other measurements at the same age, to measurements at previous ages, or to both. An example of the use of such standards in another connexion will be found elsewhere [4]. Ratios, such as Height/Weight or Height/$\sqrt[3]{\text{Weight}}$, involve either fallacy or considerable complication, and are best avoided [5].

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Dr. E. R. Bransby and Mr. W. H. Hammond: The ideal physical standard is one which would provide an *objective* measure of development: The clinician would not need to interpret the growth data, but would try to find the cause of any poor development. The next best method is to present the growth data to the clinician in a form which he can readily understand, as a diagnostic aid in his examination of the child.

Any physical standard, before being recommended for general use, requires thorough testing. It is not sufficient simply to set statistical limits of normality; a standard must stand up to clinical test. These can be of two kinds, first on representative groups of children, to assess the validity of the standard when generally applied, and second in cases with recognized pathological conditions in which the change in relation to the standard is related to clinical progress. A standard may be able to select children with a rapid loss of weight as may occur in certain conditions, but fail to select those affected by long-term under-nutrition.

Physical standards can be divided into the static and the dynamic, the former based on a single set of measurements taken at one time, the latter on series of measurements taken at intervals. Static assessments relate generally to the degree of underweight, dynamic assess-ments to the rate of growth. Assessment of the development of an individual requires a standard or normal for that individual with which to compare his actual development. The aim is to find which measurements and which combination of them give the best prediction of the normal. This process is well illustrated by the search for suitable static standards.

Comparison of a child's weight and height with the "average" for his age can only show whether the child is at or above or below average. The practice is growing of setting a range about the average, outside of which represents subnormality. Lim and Benjamin (1950), for example, recommend screening at a 15% weight for age deficiency or a certain retardation in height and weight for age. Such a screen will allow light, healthy children to fall below, and underweight children to remain within the normal range. The heavier the child, the greater the degree of underweight for it to fall outside the normal range.

Standards of $\frac{W}{H}$ for age have been widely used. $\frac{W}{H}$ agrees fairly well with the physical type distinction based on other factors, and as a result leptosomes will have a low and pyknics a high $\frac{W}{H}$ ratio. Moreover, both height and weight may be reduced by malnutrition, with the result that an undernourished child may still come within the normal range.

Lim and Benjamin (1950) present some interesting data from which to compare the efficacy of screens based on weight for age and weight for height for age for selecting children attending L.C.C. Nutrition Centres. They report that children attending Nutrition Centres are 2·4% under standard height and 15% under standard weight. A screen of a 15% deficiency in weight for height selected 39%, and that of a 15% deficiency in weight selected 51% of the children. On the other hand, the weight for height screen will select about 3%, and the weight screen about 10% of a random group of children (calculated on a 12% coefficient of variation). A 15% deficiency in weight screened 51 of 100 children attending the Nutrition Centre; the same number are screened by a deficiency of about 12·5% in weight for height. 45 of the 51 children were selected by both screens, leaving 12 selected by one, but not the other screen. It would be interesting to know whether it was clinically certain that the 45 children were malnourished, and whether the clinical diagnosis in the case of 12 children supported one standard in preference to the other. In comparing the efficacy of the two screens the crucial point is that they can be adjusted to select the same proportion of children attending Nutrition Centres, but, if so, the weight screen will also include more healthy children than will the weight for height screen. On these grounds, the weight for height screen is preferable. What is, however, certain is that both screens will let slip many children who ought to be selected and vice versa.

We have approached the problem of assessing underweight by trying to find the measure-ments on which to base the prediction of a child's normal weight for skeletal size. We took 20–30 measurements on about 3,000 children coming from council schools and from prepar-tory and public schools. Four measurements, namely height, chest circumference, inter-trochanteric width and knee girth were highly correlated with weight, and could be combined into regression equations, which gave a prediction of standard weights, within narrow limits. McCloy (1936, 1938) had previously used a similar technique, and had selected four measure-ments, namely, standing height, chest circumference (corrected for subcutaneous tissue), hip width (corrected for subcutaneous tissue) and knee width as the basis of prediction of

"normal weight for body build". The Harvard Growth Study (Dearborn and Rathney, 1941) devised a weight prediction formula for 16-year-old children based on chest depth, chest width, standing height, iliac width. It is encouraging to find that our calculations and those of McCloy and the Harvard Growth Study give essentially the same kind of measurements for prediction purposes.

It must be clear what such weight prediction formulæ mean. They show standard weights for certain body measurements, but these measurements may themselves be affected by health conditions. The further point arises as to whether such formulæ can select the same children as are assessed of poor nutrition or poor general condition on clinical grounds. This requires testing. We have recently obtained the assessments of nutrition or general condition of a group of children by a number of clinicians and we hope to compare the assessment of underweight from the formulæ with their clinical assessments. It would also be useful to test the formulæ in pathological cases.

The curve of growth falls into four parts, the rapid post-natal increase, the steady gain during childhood, the puberty spurt and the post-puberty decline. These phases have marked individual variations in timing, degree and intensity. Growth is complex and it is hard to believe that any child will over long periods follow a predetermined path, unless wide zones of fluctuation are set, too insensitive to detect even relatively substantial retardations.

Two dynamic indices based on the weight/height relationship, namely, Wetzel's Grid (Wetzel, 1941) and Tuxford's Index (Tuxford, 1917, 1939, 1942), call for comment. Wetzel's Grid has created much interest both here and abroad. The "channel" in which a child is originally placed is determined by his weight and height which depend both on body build and the state of health. It would seem that a child might continue in the same channel though chronically undernourished, although Dreizen, Mann and Spies (1948) report that undernourished children progress across and not along the channels. Wetzel (1941) claims that actual tests showed good agreement between ratings by the grid and by physicians, and Dreizen *et al.* (1948) also found good agreement when comparing children of good nutrition with children with nutritive failure. Bransby (1945*c*) and Leeson, McHenry and Mosley (1947), however, found that there was considerable discrepancy between health assessments made from the curves on the grid and from medical data. Stuart and Meredith (1946) report that "one not infrequently finds children who change grid channel without being able to obtain evidence ... of nutritional or other episodes which might be considered accountable".

Tuxford's Index consists of two parts, namely, $\frac{W}{H}$ and an adjustment for age. The latter is a device for bringing the Index back to 1·0 at average heights and weights at all ages.

The Index had often been used statically, but Tuxford was emphatic that it was the change of Index which was important, recommending that a loss of 1% and certainly 2% should be investigated. Interest in Tuxford's Index was largely due to the studies by Huws Jones (1938), who said that it could, equally as well as an ordinary school doctor, pick out boys assessed subnormal by another doctor. Considering the unreliability of the clinical assessment of nutrition this is hardly a commendation. Using the Index as a static assessment, Latsky (1942) concluded from clinical trials in South Africa, that it was hardly of value even as a rough sieve.

The chief disadvantage of Tuxford's Index—or for that matter of most ratios—is that it fails to allow for different relations between the standard deviations of the measurements at different ages. It is not enough to adjust for the means at different ages and leave the standard deviations to look after themselves. So far as we know, no comprehensive clinical trials have been made of Tuxford's Index used dynamically.

The need for physical indices is felt as strongly in the U.S. as in this country, and Stuart and Meredith (1946) have recently made recommendations on the use of body measurements in the school health programme. Their proposal is that the child's measurements over a period should be plotted on percentile charts, the measurements suggested being weight, height, chest circumference, hip width, leg (calf) girth and subcutaneous tissue. When used over a period the chart will show whether a child is remaining in the same position in regard to skeletal measurements, but falling back or gaining in regard to weight. The curves require subjective interpretation by the clinician, as no limits of allowable variations are set. Although Stuart and Meredith (1946) recommend six measurements, the method can be applied to fewer, say weight and subcutaneous tissue, which are quickly affected by fluctuations in health and height, and another skeletal measurement, say, hip width, which are not so readily affected. Percentile charts are simple to use, and present the data to the clinician in a convenient form.

Short-term fluctuations in growth seem to have some promise as a basis of dynamic assessment. In this country weight growth is maximal in autumn and minimal in spring. Growth in height is broadly the converse of that of weight. Bransby (1945*a* and *b*) and Dreizen, Mann and Spies (1948) have shown that the seasonal variation in weight growth is affected by the state of health. It ought not to be too difficult to set limits of weight growth in the various seasons, or school terms for children of different ages or sizes. Lim and

Benjamin (1950) make the useful suggestion that children should be screened who fail to gain weight over six months, although it must be recognized that failure to gain in the good growing periods may be more serious than failure in the less good growing periods.

The data collected on the 3,000 children referred to above were used in an attempt to find a way of predicting annual weight gain, but the results so far are generally disappointing. Correlation coefficients between the original measurements and the annual weight gains were on the whole low, averaging around 0·3 up to ages of 9 or 10 years, and thereafter becoming negative or variable around puberty. This complicated result was undoubtedly due to the changing rates of growth before, at and after puberty. Measurements of subcutaneous tissue may well prove of value. We have found that a single observer has a good degree of consistency in measuring, but that many observers may have considerable discrepancies. From measurements of subcutaneous tissue and body weight taken on children monthly for a year, we found that on the average the changes in both went practically together. We also found that children attending public and preparatory schools had less subcutaneous tissue than children of the same age attending council schools. Moreover, the amount of subcutaneous tissue appears to be closely associated with body type. It is doubtful if single measurements of subcutaneous tissue are of any real diagnostic value, whereas a series of measurements over a period may well prove useful.

To obtain good prediction of growth probably requires information on maturity, size and body type. It would be of great assistance to be able to assess maturity level at any age, but one difficulty is that radiographs from which to assess skeletal age are not generally practicable. Other indications are the secondary sex characteristics and the changing proportions of the body. What is required is some ratio between body measurements which is unaffected by health conditions but which is a reliable indication of skeletal maturity. The same applies to size and body type. If these combinations of measurements could be found it should be possible to account for a low weight as being due to small size, a particular body type, immaturity, or to health conditions.

We have been experimenting with the measurement of body type so that the growth of an individual can be compared with that of children of the same type. We have found that as determined from the measurements we took, type remains constant after an interval of three years. We are attempting to find a simple method of determining body type, and are examining the extent to which growth, especially in weight, is affected by type.

The immediate practical problem is how the clinician in hospital or the public health service can determine whether or not a child is developing normally and what simple screen can be used in the school health service. It is clear that there is no certain objective method. A series of measurements taken over a period are more valuable than a single set of measurements, and percentile charts are likely to prove useful. They would be much more useful if limits of normal variation could be set. The other dynamic standards require proper testing in this country against clinical data. The methods of static assessment are indeed meagre and the best that can be done is for the clinician to interpret the body measurements in association with other diagnostic material and decide whether a low weight is due to genetic or medical causes. The standards which might be considered are weight for age, weight for height for age and percentile position. The only screens at present available to the school health service are weight for age and weight for height for age.

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Dr. Cecile Asher: *Birth-weight and physical development.*—The importance of the birth-weight has recently been stressed in determining growth patterns. Attention has been drawn in this country to the relationship between birth-weight and subsequent physical development. In Sheffield, Illingworth found that children who were heavy at birth tended to remain heavy

throughout school life, and that children who were light at birth, tended to remain light. An investigation on Finchley school children has recently been completed by myself, and the same relationship is found to exist.

It has been suggested that a series of growth curves might be constructed, for children of different birth-weights. In the case of small babies it is evident that a mixed group exists. For example, a 4½ lb. baby may be full term; it may be a baby which was meant to weigh 6 lb. at birth, which was born at 38 weeks, or a 6½ lb. baby born at 37 weeks, or even an 8 lb. baby born at 32 weeks. It is obviously impossible to establish a standard curve for such a baby.

It is well known that a small baby tends to gain weight more quickly in the first few weeks of life than the average-sized baby, provided that it has not been unduly upset by the shock of being born too soon. Small babies not infrequently gain as much as half a pound a week, which is the fœtal rate in the last four weeks before birth. Babies who gain at this rate may be considered to have been born before their time. On the other hand, the small *full-term* baby gains slowly; there is no initial spurt.

The babies which are heavier than the average at birth, may be post-mature, but most of them are born of large parents; they are not only heavy, but tall. A standard curve for babies heavier than the average weight at birth would be more useful than a curve for small ones. The relationship between birth-weight and physical development is of the utmost importance; it is one of the points to be taken into consideration in determining if any particular child is below weight and height for his age.

In trying to determine if the weight of a child is within normal limits, several factors need to be taken into consideration, namely, birth-weight, stature of relatives, average height for age, average weight for age, average weight for height. Age is also important, as it is necessary to know if the child is at a springing up or a filling-out period of growth. A clinical examination of the child should reveal if the child is in good health or not. All these points have to be considered, before an attempt can be made to assess the child's degree of normality.

Dr. J. W. B. Douglas: *The weights and heights of a national sample of 2-year-old children.* —In the Maternity Survey of 1946[1] birth-weights were obtained for 13,257 babies born during the week March 3–9 in all parts of Great Britain. Two years later 4,098 of these same babies[2] were revisited and their weights and heights recorded. In addition detailed questions were asked about their health and development and the social and economic conditions in which they were growing up. A description of these two surveys has been published elsewhere [1, 2].

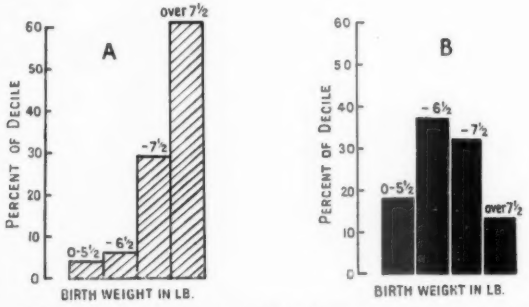


DIAGRAM 1.—Birth-weights of (A) the heaviest 10% of 2-year-old children and (B) the lightest 10% of 2-year-old children (First children only.)

Using the measurements collected in these two surveys, an analysis has been made of the relation of the weight of 2-year-old children to various social, medical and biological factors of which the most noteworthy were social class, maternal efficiency, overcrowding, lower respiratory infection, type of infant feeding, birth order, sex, and weight at birth. With the exception of lower respiratory infections all these factors were significantly correlated with weight at 2 years; but it has not been possible to show that even repeated attacks of bronchitis

[1]This survey was carried out by the Joint Committee of the Royal College of Obstetricians and Gynæcologists and the Population Investigation Committee under the Chairmanship of Professor James Young. Funds were provided by the Nuffield Foundation and the National Birthday Trust Fund. The Institute of Child Health took part in the 1948 follow-up survey.

[2]For the survey at 2 years only one in every four working-class babies in the maternity survey sample was taken. Babies in other social classes were fully sampled.

or pneumonia were associated with low weights or stunted growth. Moreover the significant correlations with the other seven factors listed above were of small magnitude and together explained only a small part (less than 10%) of the total variation in the weight of 2-year-old children. Only social class, sex, overcrowding, birth order and birth-weight were significantly correlated with height and, together, they accounted for approximately 4% of the total variation between individual heights.

Birth-weight was about four times as effective in predicting weight at 2 years as any of the other factors studied; but, even so, it will be seen in Diagram 1 that a not inconsiderable proportion of babies of light birth-weight were in the heaviest group at 2 years and, conversely, that some of the babies who were heaviest at birth were among the lightest at 2 years.

It would seem that no method of selection of 2-year-old children based on height or weight alone or any combination of these measurements can be effectively used to isolate those who have suffered from ill-health, poor home conditions or inefficient maternal care. Nor is it possible to make any accurate prediction of the weight or height of a child at 2 years from his weight at birth and a knowledge of the type of environment in which he will grow up.

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[*May* 12, 1950]

Meeting Held at the Queen Elizabeth Hospital for Children, Banstead Wood, Surrey

Five Cases of Cystic Fibrosis of the Pancreas

Of this group of five cases three were diagnosed during the neonatal period; the fourth at six months and the fifth at the age of 1 5/12 years.

Diagnosis in each case has been confirmed by examination of duodenal fluid obtained by duodenal intubation, the position of the tube being confirmed by X-ray examination. Treatment has consisted of:

(1) Diet (high calorie, high protein, moderate starch, low fat).
(2) Vitamin supplements in large doses.
(3) Pancreatin 0·5–1·0 gramme with feeds, amount being controlled by presence of trypsin in the stools (exception Christopher S.).

None of these children has chronic pulmonary disease, although the two who were diagnosed late have each had repeated attacks of respiratory infection. Graham B., who has had persistent abdominal distension due to malrotation of the bowel, has also had pneumonia on several occasions. In this patient the abdominal distension may have been an ætiological factor.

Checks on effectiveness of treatment are:

(1) Rate of growth and increase in height.
(2) Presence or absence of abdominal distension.
(3) Examination of stools for bulk
steatorrhœa, starch } detected by microscopic examination of fresh specimens.
trypsin if pancreatin is being given.
(4) Freedom or otherwise from lung infection.

Mary J. Wilmers, M.D., M.R.C.P.

Case I.—Carol D. Date of birth 27.2.50. Now 2½ months.

History.—First child of normal parents. Birth-weight 5 lb. 11¾ oz. First seen at the age of 11 days because of failure to regain birth-weight.

Examination and diagnosis.—Weight 5 lb. 1½ oz. Breast milk was insufficient, but in spite of complementing to adequate calorie intake, the weight remained around 5 lb. and stools were frequent although normal in appearance. At the age of 3 weeks a diagnosis of fibrocystic disease was considered. A stool was examined for fat and showed fat globules in great excess. The diagnosis was confirmed by finding no tryptic activity in the stools on April 4 (repeated examinations) and by duodenal intubation done on April 5, which showed no tryptic or diastase activity in the duodenal juice.

Response to treatment.—On April 8 she was started on a supplement of Casydrol and glucose in expressed breast milk bringing the total calorie intake up to 100 calories per lb. and protein intake to between 3 and 4 grammes per lb. body-weight daily. Full doses of vitamin supplements have also been given. Weight 5 lb. 2 oz. when treatment started 8.4.50,

rising to 6 lb. 2 oz. on 18.4.50. Pancreatin by mouth started on April 21, in dosage of ½ gramme with each feed. Weight on May 2, 6 lb. 12 oz.

CATHERINE A. NEILL, M.D., M.R.C.P. (for HELEN M. M. MACKAY, F.R.C.P.).

Case II.—Christine D. Date of birth 28.5.49. Birth-weight 7 lb. 2¼ oz. Now 11/12 year. Weight 19 lb. 14½ oz.

History.—First child, parents healthy, no relevant family history. Born at Mothers' Hospital Clapton. Loose stools from 3 days old—4–8 a day, moderate size, green homogeneous appearance. Diagnosed as probable gastro-enteritis and at 7 days put on water only twenty-four hours, then calories increased: failed to gain on 380 cals. daily, being 15½ oz. below birth-weight at 10 days, 14½ oz. below at 21 days. She was restless and hungry.

Investigations.—A. *Stool for trypsin* (1) Before treatment—4 specimens negative. (2) While on pancreatin powder (2·5 grammes daily) trypsin present 1/62–1/128 dilution. (3) After stopping pancreatin for forty-eight hours no trypsin (5.4.50). B. *Duodenal juice* 21.6.49. No trypsin. (Confirmed March 1950 with X-ray control.) C. *Stool for Fat* (1) 18.6.49 (twenty-four hours). Intake approx. 16 grammes, output at least 5·8 grammes fat, metabolized 64% or less. Fat globules+++. (2) While on diet with pancreatin, fat globules absent or scanty. (3) After stopping pancreatin for forty-eight hours fat globules +++(29.7.49 and 3.4.50).

D. *Stool for nitrogen* (single specimens only, urine free):

(1) November 1949.—1·79 grammes nitrogen per 100 g. fæces:

(2) April 1950.—(off pancreatin for forty-eight hours) 2·84 grammes N. in 120 g. fæces (24 hour specimen),

X-rays chest: No abnormality—June 1949, September 1949 and November 1949.

Diagnosis.—Confirmed at twenty-one days. *Treatment*: Started on (1) high calorie, high protein supplements after breast feeds and (2) pancreatin powder at twenty-seven days.

Progress.—Very satisfactory. Chest infections: mild bronchitis July 1949, September 1949, November 1949, March 1950, all treated oral penicillin at home for three or four days (mother given supply). Stools: 2–4 a day, slightly offensive, not loose.

Age	Wt. lb.	Wt. oz.	Feeds given	Cals.	Cals./lb.	Protein (grammes) (*a*) Total	Protein (grammes) (*b*) Hydrolysed
1/12	7	9	Breast (18oz.) + Sep. Lacidac with Casydrol and sugar	540	72	19·2	6
3/12	11	9	As before	670	65	29·4	9·0
4/12 to 5/12			Breast milk failed slowly				
5½/12	14	8	½cr. National Dried Milk. Casydrol Sugar	775	54	40	20
From 6/12			Solids introduced gradually.				
11/12	19	14¼	Now on lean meat (1 ration per week), fish, lean bacon, cheese. 3 eggs per week, potato 1 tablespoon daily, bananas 3 per week, banana powder dr. ii daily, green vegetables, fruit. Bread 1 slice daily.				

Milk feeds.—½ cr. N.D.M. 6 measures, Casydrol 1½ dr., sugar 3 dr., t.d.s.

Pancreatin.—0·5 gramme 6 times daily in feeds till 4/12.
,, 5 ,, ,, ,, ,, ,, 7½/12.
,, 4 ,, ,, ,, ,, ,, 9/12.
,, 3 ,, ,, ,, ,, ,, present date.

Vitamins, &c.—Radiostoleum ℔ 20 daily from 1/12. Vit. A. conc. 5,000 units daily from 5/12 (previously given to mother). Crude liver (B.P.) dr. i daily from 5/12. Becosym. tab. i daily from 5/12. Ascorbic Ac. mg. 50, Ferrous sulph grains 9 daily.

Present condition.—Well, abdomen very slightly distended, no other abnormality.

Diet: Mother supplied with measures calibrated to contain known weights of each substance in the milk mixture. Pancreatin given in powders weighed out in separate papers by dispensary.

P. RASHBASS, M.B., B.S., D.C.H. (for HELEN MACKAY, F.R.C.P.).

Case III.—*Cystic fibrosis of pancreas presenting as intestinal obstruction.*

Graham B. Date of birth 12.7.49. Now 10 months old.

History.—Second child; first normal. At birth œdematous, weight 7 lb. 1 oz., abdomen was distended. X-ray examination showed intestinal obstruction. Bile-stained fluid was vomited and no meconium was passed up to time of operation.

Laparotomy for relief of intestinal obstruction at 20 hours of age by Mr. U. A. J. Swain. There appeared to be a volvulus of small intestine—irreducible because of dense adhesions to anterior abdominal wall. Obstruction relieved by ileo-colic anastomosis. The meconium was very viscid.

Diagnosis of cystic fibrosis of pancreas suggested by viscid meconium found at operation. Meconium ileus was presumably the primary cause of obstruction. Diagnosis confirmed by absence of trypsin in stools (2 specimens) and in the duodenal juice.

Subsequent treatment and progress.—Regular weight gain achieved until 4 months of age by high calorie diet containing little fat and high proportion of protein, part of which was hydrolysed casein. Pancreatin 1 gramme with feeds, and large doses of vitamin supplements have been given throughout life. Diet has been on similar lines to that given to Christine D. (*see above*).

Weight at 3 weeks	5 lb. 12 oz.
Weight at 4 months	11 lb. 5 oz.
Weight at 9½ months	13 lb. 3 oz.

Complications have been: (*a*) Persistent gross abdominal distension, often also visible intestinal peristalsis. (*b*) Recurrent upper respiratory and pulmonary infections; pneumonia on 3 occasions treated in this hospital.

X-ray examination after barium meal suggests that only half of small intestine is functioning and that this leads into the descending colon, the rest of the small intestine and of the large intestine being short-circuited.

Child is embarrassed by abdominal distension which may be a factor predisposing to pulmonary infections. These have severely retarded progress since the age of 4 months. There is no X-ray evidence of chronic lesions in the lungs.

W. F. Young, M.D. (for I. M. Anderson, M.D., M.R.C.P.).

Case IV.—Lynn G. Date of birth 8.11.49. Now aged 6 months.

Family history.—First child. Father has pulmonary tuberculosis.

History.—Full-term infant, normal delivery. Birth-weight 7 lb. 1 oz. Mother had toxæmia of pregnancy. Breast fed up till the age of 3 months—weight 10 lb. 12 oz. Baby was admitted to Ilford Isolation Hospital suffering from gastro-enteritis and respiratory infection. X-ray showed area of consolidation in left lung. Treated with penicillin, sulphonamides, streptomycin and chloromycetin. Pulmonary infection controlled after long course but cough has persisted. Stools have remained offensive, despite frequent regrading of feeds for diarrhœa. Prolac 1 in 12 (1·6% fat) was noticed to be tolerated better than full-cream feeds.

7.4.50: *Transferred to Banstead* at the age of 5 months.

Examination.—Small, poorly nourished infant (weight 9 lb. 13 oz.). Abdomen rather distended, but child took feeds well. Stools large and offensive. No physical signs of pulmonary disease.

Investigations.—Mantoux negative. X-ray chest: Lung markings of both lower lobes increased and small patch of pneumonitis left lower lobe (no consolidation). Swabs from tonsils: *Staph. aureus.* Stools: Fæcal trypsin absent in three specimens (8.4.50–19.4.50). Duodenal juice (20.4.50): Trace only of trypsin present. Repeated (5.5.50): Trypsin absent.

Progress.—Following admission the stools were very bulky and offensive. Abdomen became rather less distended and the baby lost 3 oz. during the first five days. She has a persistent harsh cough.

21.4.50: High calorie, high protein, low fat diet (cals. 765 and protein 48 grammes per day) and high vitamin intake commenced.

28.4.50: No gain in weight. Pancreatin was started. Progress is indefinite so far.

Pamela B. Reid, M.B. Ch.B. (for I. M. Anderson, M.D., M.R.C.P.).

Case V.—Christopher S. Date of birth 8.8.46.

History.—(1) Flat weight curve from 1–2 years of age. Birth-weight 7¾ lb. (8.8.46); at 1 year 19 lb.; at 2 years 19 lb.; at 3 years 8 months 35½ lb.

(2) Recurrent respiratory infections from 3/12–1 10/12 years.

(3) Multiple severe herniæ repaired during first 14/12 of life.

(4) Food intolerance dating ? from 4/12 when mother first noted that stools were offensive. On admission to Q.E.H., Shadwell, aged 16/12 in Febuary 1948, lean buttocks, protuberant abdomen and bulky, offensive greasy stools were noted. Transferred to Banstead June 1948. Diagnosis of cystic fibrosis of the pancreas was established by duodenal intubation and examination of aspirated fluid for trypsin in November 1948. Strict diet (low fat, low starch, high protein) and liquor pancreatin dr. ½ (containing only ·03 gramme per dose) t.d.s. were given from July and August 1948 respectively. Subsequently the patient gained weight satisfactorily and was free from serious respiratory tract infections. He was admitted to

Q.E.H., Hackney, on 21.3.50 for confirmation of the diagnosis by duodenal intubation.

Examination.—Weight 35½ lb. Plump active boy with rosy cheeks. Moderate degree of knock-knee. Slight abdominal distension. Definite slight clubbing of fingers, but not of toes.

Tests to verify diagnosis of cystic fibrosis of pancreas:

(1) *Response to full ward diet* 22.3.50–25.3.50 (without pancreatin). Diet was calculated to contain 1,493 calories, 65 grammes fat and 62 grammes protein daily.

(*a*) Single stool (urine free) 24.3.50, analysed for nitrogen: Weight 305 grammes, nitrogen 6·0 grammes (equivalent to 38 grammes protein in one day). The result of this test showed that protein was not being absorbed well by the alimentary tract.

(*b*) Microscopy of same stool showed fat globules ++++ and these persisted on repeated examinations.

(*c*) Analysis of three days' stools showed that 67·7% of fat was metabolized (normal greater than 90%).

(2) *Duodenal juice*, 24.3.50: Fluid obtained was heavily bile-stained pH 6·3. Trypsin *not* detected.

(3) *Fæcal trypsin*, 24.3.50 and 8.4.50. Trypsin absent.

There were signs of intolerance (diarrhœa, abdominal distension and general irritability) on 25.3.50 and a more restricted diet (similar to his recent regime at home) was given. This was well tolerated.

Diet calculated to contain 1,508 cals., 34 grammes fat and 81 grammes protein daily.

Investigations:

(*a*) Three days' stools (not entirely urine free) analysed for nitrogen: Weight 294 grammes, nitrogen 7·4 grammes (equivalent to 46 grammes of protein in 3 days). The above result suggests that restriction of fat had improved absorption of protein by the alimentary tract.

(*b*) Microscopy of stool showed fat globules++.

(*c*) Analysis of three days' stools showed that 79·2% of fat was metabolized.

Other investigations.—Blood chemistry: Serum inorganic phosphorus 3·4 mg.%; serum alkaline phosphatase 6 units; serum urea 27 mg.%; serum calcium 10·5 mg.%.

X-ray (1) Wrist: Bone age appears to be within normal limits, and there is no evidence of definite rickets. (2) Chest: Lung fields appear clear.

Present treatment.—(1) Glycerin pancreatin (10% pancreatin) dr. 1½ (containing about ½ gramme pancreatin per dose) with meals t.d.s. was started on 12.3.50. Stools examined 17.3.50 showed trypsin in dilution of 1 in 2 (very weak concentration). The dose was therefore increased to dr. 3 (containing 1·0 gramme pancreatin) with meals t.d.s.

(2) Diet to supply high calorie, low fat, moderate starch and high protein. One pint is allowed ½ sk. fresh milk (cream removed by boiling) daily and unlimited skimmed milk, 1 egg daily (to be increased to 2 if tolerated), unrestricted amounts of lean meat and fish, and vegetables with low starch content. One small to average helping of starch-containing food with each meal, e.g toast at breakfast and tea. Potato *or* rice pudding at lunch and supper.

(3) Vitamin Supplements:

Radiostoleum	℥	10	twice daily.
Yeast tab.		1	
Benerva Co. tab.		2	
Ascorbic acid		50 mg.	
Ext. hepat liq.		1 dr.	

Thrombocytopenic Purpura in a Mother and Newborn Child.—DAVID MORRIS, M.R.C.P., D.C.H. (for R. H. DOBBS, M.D., F.R.C.P.).

E. S., full-term male infant, birth weight 8 lb. 7 oz., born at the City of London Maternity Hospital, 25.2.50.

At birth, patchy petechial eruption on chest and groins with bruising of feet. Synkavit 10 mg. was given repeatedly.

Mother, aged 27.

Obstetric history.—Normal. First pregnancy normal; healthy boy aged 4 years. Second pregnancy normal but there had been bruising of ankles and shins beginning at sixth month. Moderate APH. Severe PPH. Transfused with 2 pints blood. After delivery considerable bruising and ecchymoses of shins and ankles. No purpura elsewhere. Liver and spleen not palpable.

4.3.50: R.B.C. 4,000,000; Hb 75%; platelets 150,000.

Discharged on 5.3.50 at own request still showing bruising.

23.3.50: Started to bleed P.V. and continued till admitted to London Hospital suffering from severe blood loss on 30.3.50.

31.3.50: Hb 47%. Platelets v. occasional. Bleeding time 10 min. ++. Transfused 3½ pints blood.

2.4.50: Hb 86%. B.T. 9 min. 45 sec.
3.4.50: Platelets 6,000. B.T. 10 min.
12.4.50: Hb 77%. No platelets seen. B.T. 10 min. ++.
18.4.50: Discharged home. Failed to reattend for further blood examinations till 5.5.50: R.B.C. 4,900,000; Hb 90%; platelets; 9,800. B.T. 23 min. 35 sec. Fresh bruising, patchy purpuric eruption. Slight oozing of blood from gums.

Infant.

25.2.50: R.B.C. 4,500,000; Hb 110%; platelets 35,000.
29.2.50: Passed small amount of blood intimately mixed with stool and meconium. Passed pinkish red urine for next three days which even on immediate examination showed no R.B.C. but gave strongly positive guaiac reaction.
Whilst in hospital the bruising of feet gradually faded and small fresh crops of purpura appeared from time to time on groins and thighs. Clinically a well and vigorous child.
4.3.50: R.B.C. 6,500,000; Hb 112%; platelets 255,000.
Admitted with mother to London Hospital 30.3.50. Few new ecchymoses on leg and profuse petechiæ on soft palate.
31.3.50: R.B.C. 3,300,000; Hb 63%; platelets 6,600. B.T. 10 min. +. Coag. time 3 min. 54 sec.
3.4.50: R.B.C. 3,260,000; Hb 60%; no platelets. B.T. 10 min. Retic. 16·4%.
5.4.50: R.B.C. 3,500,000; Hb 66%; platelets 24,000.
6.4.50: R.B.C. 3,500,000; Hb 65%; platelets 7,000. B.T. 10 min. +.
8.4.50: R.B.C. 3,200,000; Hb 60%; platelets 3,200.
11.4.50: R.B.C. 2,900,000; Platelets 8,700.
18.4.50: Tibial marrow puncture showed a normal marrow. Megakaryocytes normal in number and appearance.
5.5.50: R.B.C. 4,060,000; Hb 77%; platelets 400,000. B.T. 1 min. 20 sec.
Subsequently (August 1950) infant progressed normally with normal platelet levels. Mother remained with moderate thrombocytopenia.

Thrombocytopenic Purpura in Infancy.—L. J. LETTY, M.B., B.S. (for Dr. H. M. M. MACKAY, M.D., F.R.C.P.).

D. B. Born 2.8.49.

Normal home delivery. Normal pregnancy. Birth-weight 5 lb. 8 oz. Admitted to Mothers' Hospital, Clapton, when 24 hours old with anæmia. Hb 60%. No cause found. Blood group A. Rh positive. Transfused once. Discharged at 9 days. Failed to attend for follow-up.

Reported well except for gradually increasing pallor until 7 weeks old.

Family history.—Parents and one brother well. No blood disease in family. No abnormality in examination of parents' blood.

On admission to Q.E.H. (22.9.49).—Weight 8 lb. Had passed 3 stools with bright blood. Fontanelle depressed. Widespread petechiæ. Hb 50%. Liver and spleen not palpable. Transfused with 160 c.c. fresh blood. Blood culture—*Staph. albus* (Coag. neg.) presumably contaminant. W.R. and Kahn negative. Following transfusion Hb 119%. Platelets 41,000. Bleeding time normal. Given Synkavit 10 mg. daily and penicillin for left otitis media.

Progress.—By third day—petechiæ clearing, no blood in stools, spleen just palpable. Sixth day—few fresh petechiæ on wrist, prolonged bleeding from injection sites. Transfused 20 c.c. fresh blood. Spontaneous bleeding continued from drip wound and heel prick for four days till tenth day when Hb 70% and platelets 16,000. Bleeding time over ten minutes. Twentieth day—very pale. No bleeding. Hb 48%. Platelets 30,000. Tibial marrow puncture performed. Comment on puncture: "It is very probable that the differential marrow count has been vitiated by the presence of an excessive amount of peripheral blood. Leukæmia may be excluded, but it is doubtful whether any other conclusion can be drawn. No megakaryocytes seen in cells counted (400)."

Fresh blood 180 c.c. given.

For the next three weeks platelets rose steadily to 93,000 and Hb remained between 76% and 92%. Bleeding time became normal (3 min.).

On fortieth day (October 30) developed severe gastro-enteritis necessitating intravenous therapy. Platelets fell and continued falling until three days after 90 c.c. blood given when platelets were 42,000. Hb 66% but no recurrence of bleeding.

Spleen became impalpable after seven weeks' illness and after ten weeks she was discharged. Hb 66%. Platelets 98,000. Wt. 10 lb.

Seen two weeks and one month later—anæmia unchanged. Platelets 192,000. Looking slightly pale, otherwise well. Spleen impalpable.

9.5.50: 9 months of age. No further purpuric manifestations. Well. Spleen impalpable. Hb 76%. Platelets 163,000. Weight 19 lb. 6½ oz.

Retrolental Fibroplasia in a Premature Infant now aged 2 Years.—PAULINE COLE, M.B., B.S. (for J. MINTON, F.R.C.S., and I. M. ANDERSON, M.D.)

C. K., born 19.4.48.

Family history.—First child of healthy parents. No consanguinity. No previous miscarriages. No family diseases or blindness.

History.—Mother perfectly well throughout pregnancy, but went into labour 14 weeks before expected date. Normal labour.

Birth-weight 2 lb. 8 oz. Kept in Oxygenaire tent for sixteen days. Gained steadily. Fed on expressed breast milk for six weeks, then half-cream National Dried Milk, with orange juice and cod-liver oil. No other vitamin supplements.

At 2 months discharged from maternity home weighing 5 lb. 1 oz. No abnormality of the eyes noticed at this time.

At 4 months mother first noticed a "white mist" over the baby's eyes, and that she did not follow objects with her eyes.

At 9 months she was referred to Mr. Minton for ? bilateral congenital cataract, and on examination was found to have bilateral retrolental opacities and posterior synechiæ. The W.R., Kahn and gonococcal complement fixation tests were negative in serum and C.S.F. The blood count, and urine tests were within normal limits. Skull X-ray was normal.

At 2 years the baby was admitted to the Queen Elizabeth Hospital for investigation. She was then a thin but healthy child, walking well and talking a little, and did not appear mentally backward. Totally blind. Intermittent alternating convergent squint. No nystagmus. No other abnormality of C.N.S.

Examination under anæsthetic by Mr. Minton (5.5.50).

Report.—Right eye: Cornea clear and of normal dimensions. No K.P. or opacities present. Very shallow anterior chamber. The iris is atrophic at the pupillary margin. The rest of the iris has a normal pattern. The pupil is irregular, with multiple small and large posterior synechiæ adherent to the lens. The lens is clear. A grey mass is lying in the vitreous a good way behind the lens. This is most probably a detached retina. With an ophthalmoscope, a yellowish light reflex can be obtained from the temporal side of the detached retina. No light reflex can be obtained from the nasal side. Pressure on the temporal side of the globe causes movement of the temporal side of the detached retina. The left eye is similar, although the pupil is more dilated than the right.

Retrolental Fibroplasia in a Full-Term Infant associated with Multiple Congenital Deformities (*Photographs only*).—PAULINE COLE, M.B., B.S. (for J. MINTON, F.R.C.S., and HELEN M. M. MACKAY, M.D., F.R.C.P.)

R.N., female, born 16.9.49; died 5.2.50 from gastro-enteritis.

Family history.—Parents healthy. No consanguinity. Two previous full-term pregnancies. One child now alive and normal, aged 6.

History.—Birth-weight 6 lb. 12 oz. Congenital micrognathia, cleft palate and talipes equinovarus. Bilateral retrolental opacities first noticed at 5 weeks. At 3 months, white vascular masses present behind lens in both eyes, probable detached retinæ. No posterior synechiæ.

Photographs of eye sections shown, with report by Dr. N. Ashton.

This was probably a case of Krause's "encephalo-ophthalmic dysplasia".

Eh'ers-Danlos Syndrome.—J. N. O'REILLY, D.M., M.R.C.P.

W. D., female, aged 6 years and 5 months.

History.—June 1948, large tear in the skin of the right shin caused by catching leg on lock of a trunk. A few weeks later large tear in the skin of the right leg following slight contact with a projecting nail, healing with a papyraceous scar. No ember 1949, large tear in the skin over right knee following a fall on a carpet.

On examination.—The child has marked hyperelasticity of the skin with a peculiar silkiness to the touch. There are large papyraceous scars on the right leg. General health good. Typical case of Ehlers-Danlos syndrome showing: (1) Familial incidence: Mother's skin is of the same silky texture, but not apparently fragile. (2) Extreme elasticity and fragility of skin. (3) Hyper-extensibility of the joints. (4) Healing of injuries with papyraceous scars. (5) Other characteristics of the syndrome are presence of nodules in the skin due to organization of hæmorrhages following trauma without tearing of the skin, and well-marked epicanthic folds.

A Demonstration of Case Photographs and Children with Cleft Lips and Palates was given by R. J. V. BATTLE, M.B.E., M.Ch., F.R.C.S., and R. P. G. SANDON, M.B., B.S.

Section of Dermatology

President—W. N. GOLDSMITH, M.D., F.R.C.P.

[*February* 16, 1950]

Prurigo Nodularis.—W. P. ELFORD, M.D., and F. PARKES WEBER, M.D.

E.U., married man of 64, a butcher, developed an eruption of small itchy papules on the legs in 1940, and subsequently on the arms and scrotum. The lesions gradually increased in size until some were the size of small grapes. More recently the lumbo-sacral region and the backs of the thighs have been affected. The lesions are sharply outlined, raised, and apparently confluent in places. The surface has a peculiar cerebriform appearance, pale-pink in colour, with a slight violaceous tint, the surrounding skin being brownish. There is no ulceration, but itching is said to be intense, and scratching causes some bleeding. The patient attributes the increase in size and the development of new lesions to scratching. None of the lesions has ever disappeared, but many new ones have gradually developed. There is no constitutional disturbance. There is a firm non-tender gland, the size of a bean, in the left inguinal region, and the right epitrochlear gland is palpable. Factitious urticaria could not be demonstrated.



FIG. 1.



FIG. 2.

FIGS. 1 and 2.—Lesions on the lower extremities.

Past history.—No illnesses. Said to have had fits as a child.

Personal history.—Married, 3 sons, aged between 32 and 39. Youngest has had fits of an epileptiform nature since the age of 2 or 3 years.

No idiosyncrasy to food. Said to have drunk considerably at one time.

Family history.—3 brothers and 2 sisters. Family split up early and lost trace of. No known history of complaints of an allergic nature in the family.

Investigations.—W.R. and Kahn reactions negative. E.S.R. (1946): 28 mm. in one hour. (1950–Jan.): 1 hour—20 mm. 2 hours—30 mm.

Mantoux reaction: 1:10,000, negative. B.P.: 155/85.

Urine: Albumin nil. Sugar nil.

Glucose tolerance test normal.

Smears: Few polymorphs. Many Gram-positive cocci, few Gram-negative bacilli and Gram-positive bacilli. Occasional thin filament. No yeast-like spores seen.

Culture: Contaminating mould. Gram-negative bacilli and Gram-positive cocci. No yeast-like spores grown.

Guinea-pig inoculation negative.

Blood-count (1946): R.B.C. 5,000,000; Hb 100%; W.B.C. 8,000. Polys. 74%, lymphos. 18%, monocytes 3%, eosinophils 5%. (1950): R.B.C. 4,700,000; Hb 95%; W.B.C. 10,000. Polys. 73%, lymphos. 21%, large monos. 4%, eosinophils 2%.

Histology (Dr. Muende).—"The epidermis shows marked warty hyperplasia. The corium contains a dense cellular infiltration with lymphocytes, few eosinophils and numerous reticulum cells."

Section stained for amyloid was negative.

Treatment.—Local applications have proved unhelpful. Oral iodides gave no relief. Superficial X-ray therapy to one leg had no apparent effect on the condition. (Dose: 150 r filtered through 3 mm. aluminium at weekly intervals for four doses.)

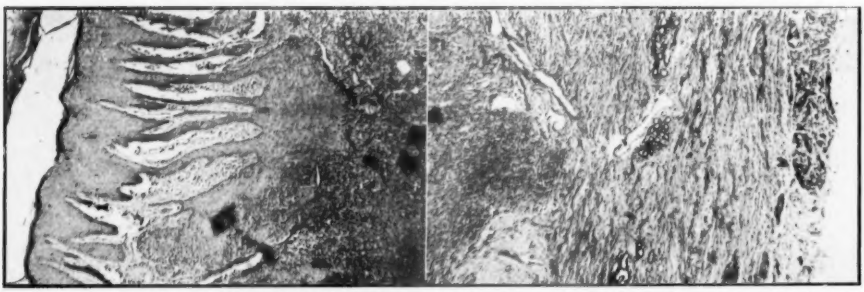


FIG. 3 (Section II).—Prurigo nodularis. High power. To show acanthotic *papillomatous* growth and nodule of granulation tissue protruding downwards and infiltrating subcutaneous fat tissue.



FIG. 4 (Section III).—Prurigo nodularis. High power. Showing the early changes in the pre-nodular phase. Marked acanthosis with no intra-epidermal œdema. Cellular infiltration around vessels with narrowed lumen and limited to the subpapillary layer.

Dr. F. Parkes Weber: I am very pleased to be associated with Dr. Elford in his search after truth; that is really what this Society is meant for. When one is seeking the truth in a puzzling dermatological case one cannot do better than bring it before this Section. Neither the doctor nor the patient can lose anything, they may gain a great deal. The present case might be an exaggerated form of prurigo nodularis, but no one seems ever to have seen an undoubted case of prurigo nodularis which looks exactly like it. That does not rule out the diagnosis completely; it might be a very rare exaggerated form. The lesions are associated in some way with the localized itching and scratching. When I spoke recently to Sir Aldo Castellani and showed him the notes he agreed that it was a case of prurigo nodularis, but when I showed him the photographs he said that though he had seen a good deal of prurigo nodularis, he had never seen a case quite like this one, which superficially reminded him of cases of chromoblastomycosis, a very unlikely disease to occur in England.

Anyhow, the nodular lesions as illustrated by the first section, are a kind of very chronic subepidermic non-suppurative granulomata, covered by wart-like thickened epidermis with (in parts) a cerebriform naked-eye appearance. Suggestions of counter-infection have been made, for instance, with wart virus.

Dr. R. T. Brain: I find it difficult to accept the diagnosis of prurigo nodularis because of the extraordinary warty appearance of the moist lesions in the groin. As a butcher he might have picked up a wart virus from one of the animals. I think one should look for inclusion bodies and it would be interesting to take a piece of the tumour and to grind it up with sterile saline and inoculate the skin with a filtrate and see if one could produce a lesion.

ADDENDUM

We are indebted to Dr. M. Lowenberg for the following histological report:

Section I.—A sessile growth on the skin; in the centre an enormous hyperkeratosis with parakeratosis, Malpighian layer very acanthotic with big cells, many binucleated ; rete pegs irregularly misshapen. A broad band of granulation tissue surrounds the acanthotic cell masses and has in places invaded them; no abscess formation present. Small tracks of the otherwise sharply limited cellular infiltration accompany vessels and sweat glands downwards. Close to the base an implantation cyst filled with lamellated horny masses and two small bits of implanted epidermis are present. [Not illustrated.]

Section II (Fig. 3).—Growth situated on a broad base. Hyperkeratosis very much less than in Section I. No parakeratosis. Epidermis raised up in a papillomatous manner with well-shaped elongated columnar rete pegs. Malpighian layer otherwise as in Section I, also a surrounding dense granulation tissue, here containing numerous eosinophils; the same invasion of the Malpighian layer without any abscess formation. The cellular infiltration protrudes much deeper, infiltrating the fat cushion of the sweat glands and the subcutaneous fat tissue.

Section III (Fig. 4).—Early Stage: Slight increase of horny layer, no parakeratosis, considerable acanthosis, no intra-epidermal œdema; amitotic dividing cells present. Collagenous tissue slightly œdematous, in one larger area sclerotic. In the upper third of the dermis a cellular infiltration of varying density mainly around the vessels, consisting of round cells, connective tissue cells, histocytes; numerous scattered mast cells, no eosinophils. Vessels mainly with narrowed lumens and endothelial swellings. No cellular infiltration in the deeper parts of dermis or in subdermis. The sweat gland coils are untwisted, their cells vacuolated, and the nuclei do not stain well. In the sub-epidermal layer only a few sweat gland ducts, not one porus sudiferus, could be found. Sebaceous glands and hairs have also disappeared.

Discussion.—The histological picture does not contradict the clinical diagnosis—Prurigo nodularis: a diagnostic histological picture for this disease does not exist. The histological findings are indefinite and multiform (Besselmann, 1932, *Arch. Derm. Syph., Berlin*, **166**, 212). This is apparent in the present case, which presents three different lesions.

The striking feature, the considerable granulation tissue, is described in the literature only in one case (Besselmann 1932), and in that case an abscess formation in the epidermis was present; rightly the author states that both conditions are neither diagnostic nor essential for the disease, prurigo nodularis. We have not seen any abscess formation but the presence of the implantation cyst shows clearly the considerable injury to the skin and the easy possibility of an infection. Examples of injured epidermis healing quickly and with considerable hyperplasia are well known in other skin diseases. The inflammatory cellular infiltration in the deeper and deepest layers is of no more diagnostic significance than the changes in the epidermis and the granulation tissue; they are secondary: in the early lesion they are missing. Even the changes in the early lesion are not characteristic; in every normal skin which is exposed to continual scratching they could be found. Whether these excessive tumour-like nodules occur without the presence of such considerable granulation tissue could not be answered from the literature, but it is striking that in Besselmann's case the nodules seem to have been as big as in the present case. The assumption of Netherton (1923, *Arch. Derm. Syph. Chicago*, **8**, 193) that the primary cause of prurigo nodularis lies in a disturbance of the sweat glands is doubtful; similar changes as described by Netherton are visible in the present case and are easily explained by the condition of the skin appendages in the upper part of the dermis.

Prurigo nodularis is mainly confused with urticaria papulosa perstans or with neurodermatitis chronica (Prurigo diathésique à grosses papules). The characteristics of both conditions are certainly not present in this case.

The assumption of an individual predisposition of the skin to react towards intensive scratching with the formation of gross papules and nodules of different histological patterns would be an explanation of the rare occurrence of prurigo nodularis.

POSTSCRIPT (October 1950).—It may be mentioned that owing to the presence (special staining methods) of peculiar lesions of the nervous elements, R. M. Perez and C. A. Maruri (*Ann. Derm. Syph., Paris*, 1949, **9**, 623) use the term "Chronic Allergic Nodular Cutaneous Polyneuritis" in preference to "Prurigo Nodularis" and the numerous other synonyms of the disease.

The following cases were also shown:

Xanthomatosis.—Dr. E. A. FAIRBURN for Dr. F. RAY BETTLEY.

Four Cases of Epithelioma Adenoides Cysticum (with photomicrographs and family trees).—Dr. C. H. WHITTLE, Dr. A. LYELL and Dr. R. E. CHURCH.

Systemic Sarcoidosis.—Dr. S. C. GOLD.

Mycosis Fungoides.—Dr. R. SCUTT.

Nævus Syringadenomatosus Papilliferum.—Dr. R. H. MEARA for Dr. G. C. WELLS.

(These cases may be published later in the *British Journal of Dermatology*.)

[*March* 16, 1950]

Spontaneous Resolution of a Molluscum Sebaceum.—L. MUSSO, M.R.C.P., for HUGH GORDON, M.C., F.R.C.P.

This patient, a woman aged 52, first noticed, eleven weeks ago, a pinhead-sized, non-painful red pimple on the right side of the neck which gradually enlarged and after five weeks became an umbilicated mass with a keratotic centre and a white, smooth, rolled edge. About six weeks ago the lower inferior third of the lesion was excised for biopsy, but the remainder of the mass continued to grow for one more week. Then it began to regress and shrank during the next three weeks to a small mass about 0·3 cm. in diameter which fell off two weeks ago. There is no history of injury and no treatment was given.

When examined on February 3 the appearance was that of a umbilicated mass with a keratotic centre and a white smooth rolled edge measuring 1·1 cm. × 0·9 cm. × 0·4 cm. high, on the right side of the neck (*see* Fig. 1). On examination on March 14, there was a red oval area measuring 2 cm. × 0·8 cm., in which the scar of the excised area could be seen, as well as a small area 0·7 cm. × 0·6 cm. of superficial keratosis at the site of the molluscum sebaceum. There are no enlarged regional glands.

Histology.—At the biopsy level the overlying epidermis is intact, and except for one tiny area of union, is separated from the lesion by a small band of connective tissue. Essentially, there is a central mass of hyperkeratosis with papillomatosis surrounded by epithelium, which for the greater part consists of an acanthotic stratum malpighii with slight atypicality of the cells. In places the basal layer is missing, and in parts the epidermodermal border of the acanthotic stratum malpighii is being disintegrated and invaded by round cells and at times eosinophils. The corium on the sides and deep aspects of the lesion is œdematous together with an infiltrate of inflammatory round cells including some eosinophils (*see* Fig. 2).



FIG. 1.—The appearance of the lesion before biopsy on February 3, 1950. (Natural size).

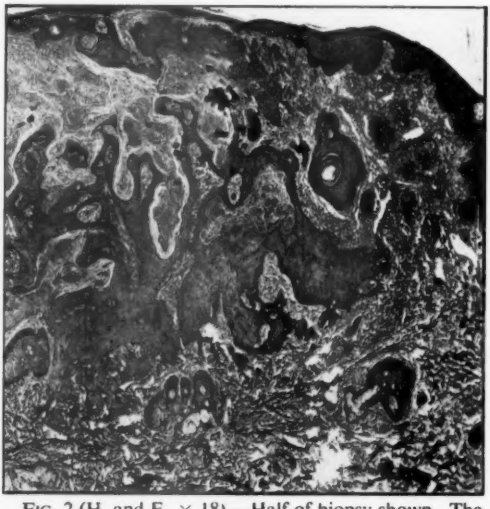


FIG. 2 (H. and E. × 18).—Half of biopsy shown. The central mass of hyperkeratosis with papillomatosis together with the acanthotic stratum malpighii is well seen. (The black marks in the upper part of the section are artefacts.)

Dr. Arthur Rook: At St. Thomas's Hospital we are satisfied that this is a clinical and pathological entity, that it is benign, and that it is to be differentiated from Grade I squamous epithelioma which it may somewhat resemble clinically, and with which it is often confused. MacCormac and Scarff (1936, *Brit. J. Derm.*, **48**, 624), in the first published account of the condition, proposed to name it molluscum sebaceum, but as this term has been employed as synonymous with molluscum contagiosum, we prefer the name kerato-acanthoma which was suggested some years ago by Dr. Freudenthal. The kerato-acanthoma usually enlarges quite rapidly for six to eight weeks, reaching a diameter of one to two centimetres; thereafter no further enlargement occurs and spontaneous regression begins. The histological evidence, which I will ask Dr. Whimster to describe, would seem to support this statement.

Most of our cases, which now number more than 40, have been treated by radiotherapy. The end-results obtained are satisfactory but the immediate response of the lesion to irradiation is less brisk than that of a basal-celled or squamous epithelioma. As our confidence in the benign nature of the kerato-acanthoma has increased, we have tended to use radiotherapy less often, preferring simple excision or even curettage in some patients. We have seen spontaneous cure occur in two cases.

Dr. I. W. Whimster: We have made a histological study of almost all the lesions mentioned by Dr. Rook and in none of them has there been any evidence of invasive growth. All the downward prolongations of epithelium seen in the lesions can be, and we think are, explained as being areas of extreme hyperplasia, probably inflammatory in origin, of sweat ducts and hair follicles. In none of these lesions have we ever seen hyperplastic epithelium lying deeper in the tissues than the normal limits of duct and follicle epithelium. Furthermore there is histological evidence that these lesions begin to regress after six to eight weeks, the epithelial hyperplasia giving place to atrophy with loss of appendages and the chronic inflammatory granulation tissue, which in the early stages forms the stroma of the lesion, to dense fibrous scar tissue. This resolution appears usually to be completed in about six months from the onset of the lesion. During the period of epithelial regression foreign body giant cells may sometimes be seen phagocytosing fragments of necrotic epithelium.

Dr. Hugh Gordon: A number of lesions identical to the one under discussion have been seen at the Royal Cancer Hospital. These have all been reported on by Professor Willis as squamous-celled carcinoma and have responded readily to standard X-ray treatment, i.e. 5,600 to 6,000 r given over a period of fourteen days.

The idea was suggested to us some time ago by St. Thomas's Hospital that a definite entity existed which they termed "molluscum sebaceum", and they held that the pathological picture could be distinguished from that of squamous-celled carcinoma. I do not propose to deal with the problem from the pathological angle, since there is as yet some difference of opinion between pathologists as to whether the differentiation from that of squamous-celled carcinoma is proved. Clinically, however, these lesions are all extremely quick growing, the history being usually under six weeks, a size of at least 1·5 cm. being attained by that date. It is held that they are non-malignant, and after attaining a certain size spontaneously regress. In this particular case, that has certainly happened.

Dr. John Ferguson Smith: I am very much interested in these cases and have seen a number of them. I have seen a case of reticulosis of the skin in an old man in which he had a number of button-like lesions, very like what is shown in this case, which underwent spontaneous regression, leaving scars. They were reported on by expert histologists as being early rather low-grade squamous epithelioma. Later on the same patient developed larger fleshier tumours which had more or less a Hodgkin's structure, but this one phase went on for about a year. I think it is quite different from those cases of multiple self-healing epitheliomata in which some at least of the early lesions have a different appearance. They are more definitely invasive, the scars are different and there is the fact that they are multiple. The whole process has gone on for so many years that one would not call it malignant in the ordinary sense; but if this response can be obtained to whatever the irritation is in mycosis fungoides (and there may be other forms of irritation of the skin which produce this picture), he would be a bold man who would say on looking at one of these sections that there was not malignancy.

Dr. C. H. Whittle: It would be interesting to learn on what parts of the body one may expect to find these growths. For instance are they in the same group as certain other lesions, usually regarded as squamous carcinomata, which appear commonly on the dorsum of the hand?

Dr. Musso, in reply to Dr. Whittle: It has been my experience that these lesions occur on the face, neck, backs of the hand and wrist areas, and Dr. R. E. Bowers had a patient with this lesion in the vicinity of the anus. There would seem to be no reason why this lesion should not occur on any part of the body. Recently, I have seen two on the left side of the nose, one situated partly on top of the other. True squamous carcinoma does occur on the dorsum of the hand, but so does molluscum sebaceum, and it would seem that cases of molluscum sebaceum have been considered squamous carcinoma in the past.

POSTSCRIPT (October 1950).—The patient who had the above lesion was examined some months later and the lesion has remained healed, showing slight scarring.

Nodular Subcutaneous Haemangiomatosis.—W. N. GOLDSMITH, M.D.

D. R., man, aged 60, of Hungarian origin.

Present condition.—Numerous subcutaneous elastic spherical tumours, chiefly on the limbs, especially shins, and on the sides of the face and neck. They vary in size up to about 2·5 cm. in diameter and are not firmly attached either to overlying skin, which looks bluish, or to the deeper tissues. There is also a profuse eruption of little red spots like petechiæ. There are also some superficial firm cutaneous papules, suggesting thrombosed angiomas. On the sides of the neck are subcutaneous strands, which feel like thrombosed vessels. The oral mucosa is unaffected.

History.—Duration about twenty years. Recently the lumps have become more numerous and some have been growing. None have disappeared.

In 1940, he had a *cerebral attack*, which lasted three weeks, attributed to a hæmorrhage which was confirmed by examination of the C.S.F. Two years later he had a *hæmoptysis*. Since then he has been in good health.

Some time ago he had what was called lupus on the side of his nose, which was treated by injections of gold.

Family history.—Nothing significant.

Investigations.—Bleeding time, clotting time, capillary fragility test, blood-count: All normal.

Skiagram of chest: Punctate calcification at the left apex and right hilar region.

Skiagram of skull: Several small, rounded translucencies in the cranial vault; some calcification in pineal and choroid plexuses of lateral ventricles.

Biopsies: A subcutaneous nodule and a portion of the firm strand on the left side of the neck were removed. Microscopical examination showed the structure of a cavernous hæmangioma without any endothelial proliferation. The walls between the cavities were perhaps rather thicker and more fibrous than usual and the cavities were stuffed full of apparently intact erythrocytes. Only in one small area Dr. Freudenthal demonstrated, by Prussian blue reaction, a little liberated iron.

Comment.—Multiple hæmangiomas fall into two groups:

(1) The mere presence in the skin of several angiomas.

(2) A profusion of mostly small angiomas over the whole body surface and involving mucous membranes and internal organs, representing probably a germ-plasm anomaly affecting the whole vascular system, which Ullmann called angiomatosis. Very rarely this is present at birth or soon after (Barber, H. W. 1931, *Brit. J. Derm.*, **43**, 131, showed a case of multiple cavernous angiomas affecting skin and oral mucosa in a baby aged 10 weeks). Generally, apart from a few telangiectases, it develops rapidly after some years (cf. senile angiomas). In the present case, the onset was at the age of about 40. Most of the published cases have been mainly telangiectases.

Clinically, the subcutaneous lumps differ from any cavernous angiomas I have previously met with in being harder, better defined, and more freely movable. As one cannot compress them, the contained blood must be almost if not quite stagnant. It is, therefore, surprising to find microscopically no sign anywhere of thrombosis.

Dr. F. Parkes Weber has suggested that the condition be called hamartomatous hæmangiomatosis, pointing out that there are other dysplastic conditions of the blood-vessels without tumour-like lumps with which hamartomata of the blood-vessels may be associated, e.g. (1) telangiectatic conditions of the skin and mucous membranes like the Osler type of telangiectasia: (2) weak spots in small arteries at the base of the brain, in the splenic circulation, and in the lungs, leading to the development of minute aneurysms and/or ruptures.

I feel, however, that hamartoma is too wide a term to bring out the distinctive features of this case.

The following cases were also shown:

Case for Diagnosis. ? Lichen Amyloidosus.—Dr. DAVID I. WILLIAMS.

Poikilodermia Atrophicans Vasculare with Mycosis Fungoides.—Dr. SYDNEY THOMSON.

Parapsoriasis en Plaques.—Dr. R. M. B. MACKENNA and Dr. E. LIPMAN-COHEN.

Calcified Epithelioma of Malherbes.—Dr. H. HABER.

Sarcoidosis.—Dr. M. FEIWEL (for Dr. G. B. MITCHELL-HEGGS).

Generalized Ecthyma.—Dr. G. C. WELLS (for Dr. W. N. GOLDSMITH).

Lymphangioma Circumscriptum and Keloids.—Dr. BRIAN RUSSELL.

Occupational Melanosis.—Dr. ARTHUR ROOK.

Pityriasis Lichenoides.—Dr. H. J. WALLACE.

(These cases may be published later in the *British Journal of Dermatology*.)

Section of Endocrinology

President—A. S. PARKES, M.A., Sc.D., F.R.S.

[*March* 22, 1950]

DISCUSSION: THE DIAGNOSIS OF DIABETES INSIPIDUS

Professor J. H. Burn: *Action of Nicotine on Diuresis*

In 1939 Dr. Mary Pickford showed that when water was given by mouth to a dog, and diuresis was fully developed, the intravenous injection of acetylcholine caused a prompt inhibition lasting forty-five minutes. If the posterior lobe of the pituitary body was then removed, and the experiment was repeated, there was no inhibition. Dr. Pickford suggested that the acetylcholine caused stimulation of the supra-optic nucleus from which impulses passed to the posterior lobe liberating the antidiuretic hormone.

Effects of acetylcholine are of two kinds, those which resemble the effects of muscarine, and those which resemble the effects of nicotine. The effects of muscarine are abolished by atropine. Since Dr. Pickford made her observations in dogs to which she had previously given atropine, I argued that the effect she observed must be a nicotine-like effect, and that it should be possible to show that nicotine possessed a similar action. Experiments were therefore carried out in rats to which water was given by stomach tube to cause a diuresis. It was found that the injection of nicotine either intravenously or subcutaneously caused an inhibition, which, however, was absent in animals from which the pituitary gland had been previously removed.

The dose injected into each rat was 0·25 mg. nicotine acid tartrate per 100 grammes body-weight. To obtain a similar effect in a man of 70 kg. it would therefore seem necessary to inject about 150 mg., which is a very large amount. In fact it was found that man is much more sensitive than the rat, because the nicotine present in the smoke of one cigarette is enough to cause inhibition of diuresis in man. The inhibition is often accompanied by a rise in the excretion of chloride, as would be expected if the inhibition is due to the release of antidiuretic hormone. The inhibition can be imitated by the intravenous injection of nicotine acid tartrate in doses from 1 to 3 mg. Different individuals vary in their sensitivity to the inhibitory actions of nicotine. Many show inhibition of diuresis only when they smoke 2 cigarettes in succession. My colleagues Drs. J. M. Walker and N. B. G. Taylor have recently demonstrated the presence of the antidiuretic hormone in the urine after smoking.

Attempts were made to determine the amount of antidiuretic hormone released in the blood by smoking. These achieved less success than we had hoped for, but we found that the smoking of one or two cigarettes released from 50 to 100 milliunits. Since the normal blood volume is about 5 litres, this corresponds to 10 to 20 milliunits per litre. Now the antidiuretic hormone is commonly believed to be identical with the pressor hormone, which causes vasoconstriction of arteries including the coronary arteries. We were therefore anxious to discover whether the hormone in a concentration of 10 to 20 milliunits per litre would exert an effect in the coronary vessels. My colleagues Dr. Edith Bülbring and Dr. J. M. Walker tested this in the heart-lung preparation of the dog, recording the flow from the

coronary sinus with a Morawitz cannula; they found that 20 milliunits in 1 litre of blood caused a diminution of coronary flow of about 10%, the effect lasting for about fifteen minutes. They were further able to show that the infusion of nicotine acid tartrate into the anæsthetized dog caused a transient increase in coronary flow followed by a slow and progressive diminution reaching a minimum in twenty minutes. This diminution could be matched by a slow intravenous infusion of pituitary posterior lobe extract.

Thus we have obtained evidence that nicotine, inhaled from cigarette smoke, liberates the antidiuretic hormone and, since this hormone is the pressor hormone, that the amount released produces some degree of coronary constriction.

Professor R. Kourilsky: *Diabetes Insipidus*

Diabetes insipidus in the human represents for most clinicians a particular kind of polyuria for which various lesions of the hypothalamo-hypophyseal tract are responsible. This condition is radically improved by the administration, either subcutaneously or by insufflation, of the extract of the posterior lobe of the pituitary. The second clinical symptom, inseparable from the former in man, i.e. thirst, is unanimously considered to be a consequence of the dehydration resulting from polyuria.

However, clinical experience recently acquired shows that the facts under observation are more complicated and that the concept usually adopted does not explain them all satisfactorily.

Our study of the question leads us to the following conclusions:

(1) Polydipsia is not necessarily the result of polyuria. Thirst and polyuria can be dissociated. This conclusion is the result of various observations. The most striking is the instantaneous amelioration of thirst, in a case of post-traumatic diabetes insipidus in a young girl of 22, during the tapping of a subarachnoid cyst at the base of the brain, which had raised the hypothalamus, and stretched the hypophyseal stem. The patient who, until then, had not ceased drinking exclaimed: "What are you doing? I am no longer thirsty." She indeed asked for no more water during the operation or afterwards. This observation is the exact counterpart of those in which the sudden appearance of the thirst was noted by the neurosurgeons (Alajouanine, de Martel, Thurel and Guillaume; Dandy 1940) without any preliminary clinically noticeable polyuria.

On the other hand, the dissociation can go still farther, and the diuresis be constantly less than the polydipsia, the surplus fluid being eliminated through the skin. This condition was noted by Kourilsky, Hinglais and Welti (1945) in a young girl, suffering from extensive tuberculosis of the hypothalamus, subsequent to a primary tuberculosis of the lung; for a year and a half diuresis continued in the constant relation of 1 : 2 to the amount of liquid absorbed.

These facts were verified during several months, with minimal error, thanks to constant medical survey day and night. At the very beginning, a condition of oligodipsia with oliguria was demonstrated; even then the dissociation between the absorption of water and output of urine already existed, but was only intermittent.

(2) The cases of diabetes insipidus in which the polydipsic factor is predominant are far more numerous than those purely emphasizing polyuria. To establish t ese facts, we resorted to the water restriction test. The patient is given a well-balanced diet low in chlorides (2,100 calories, water 789 grammes, salt 2·5 grammes). Loss of weight and diuresis are observed very carefully. The survey is made in a private room, under continual medical care day and night, and in complete isolation. The test must be interrupted if the loss of water is too severe, or if it is regular and continuous. The patient is then allowed to drink *ad libitum* and is given an injection of 10 units of extract of the posterior lobe of the pituitary gland.

Under such conditions we observed, in confirmation of Corre and Mignot (1944), that only in 16·6% of the cases did there exist a real irreducible polyuria. In 78% the restriction of fluids is, on the contrary, followed by a corresponding restriction of urinary elimination. These results confirm the data of Veil and Eric Meyer and Meyer-Bisch.

(3) Clinically and biologically, it is possible to differentiate those cases with an irreducible from those with a reducible polyuria. Our findings were checked with pathological data in typical cases. Our survey includes 38 patients.

In 4 out of 6 cases of authentic polyuria, the specific gravity of urine rose from 1001–1002 to 1008–1010 and in two it reached 1011–1013.

The posterior pituitary extract is rapidly effective and radically improves the concentration of the urine. Salt aggravates this type of diabetes to such an extent that the patient cannot tolerate fluid restriction whilst on a high salt intake which has accidentally happened in restriction tests in the past; indeed such attempts may be dangerous.

Hyperproteinæmia and hyperchloræmia are usual findings. The molar concentration of the blood reaches — 0·6° C. as measured by the Freezing Point depression during the restriction test.

Pathological findings in one of the cases demonstrated total destruction of the posterior lobe by an inflammatory granuloma, the anterior lobe being normal as well as the supra-optic nucleus.

The polydipsias fell into four groups:

(i) *Pure polydipsia of hypothalamic origin* (1 *case*).—Though the hypothalamus seemed to have been destroyed by a tuberculous infection, including the supra-optic nuclei, pituicytes were still present in the posterior lobe, and the anterior lobe was normal. This condition resulted in pure polydipsia, the ratio between intake and renal excretion of water being 1 : 2. Urine specific gravity rose to 1034–1036 during the restriction test, and diuresis fell to 60 c.c. in twenty-four hours.

(ii) *Polydipsias of pituitary origin* (28 *cases*).—Posterior lobe extract has a more or less definite action; excretion of salt is irregular, urinary concentration during the restriction relatively low (1011–1012) but, despite the restriction of water intake, there is no relative decrease in polyuria. Hyperproteinæmia is only noticeable during the restriction test, hyperchloremia inconstant. Pathological findings in 2 cases demonstrated partial destruction of the posterior pituitary lobe with conservation of many pituicytes and of the anterior lobe.

(iii) *Polydipsias of pituitary origin, reducible to normal after one or two restriction tests* (3 *cases*).—In such cases, polydipsia remained after the pituitary lesion had disappeared and polyuria had stopped. The persistence of thirst depended upon the existence of conditioned reflexes but the organic origin was beyond doubt. These cases would at first sight be considered as psychogenic.

(iv) *Pure polydipsias completely unirfluenced by treatment with posterior pituitary* (2 *cases*).—One was observed in the course of a pulmonary tuberculosis, the other in a patient with arteriosclerotic hypertension and limited softening of the brain. In spite of organic lesions of the brain, in both cases the supra-optic hypothalamic tract was normal. These cases fall into the group of "psychogenic polydipsias". This name would appear to be wrong because of the associated organic disorders.

Summary

Total destruction of the posterior lobe of the pituitary gland with conservation of the anterior lobe leads to polyuria, but in man this condition is relatively infrequent, just as is the total destruction of other endocrine glands. Partial destruction is frequent and results in reducible polyuria and persistent thirst.

Inflammatory conditions of the hypothalamus may induce thirst without apparent involvement of the posterior lobe. Thirst and polyuria are thus dissociated, though they always appear closely linked to each other in all the cases of so-called diabetes insipidus.

There are two separate regulatory functions: one is concerned with the excretion of water, the other with the intake. The latter does not result from a compensatory mechanism of dehydration, since it is present in most of the cases where general dehydration of the human organism cannot be demonstrated.

When thirst is associated with true polyuria, posterior lobe extract works instantaneously on the polyuria and only after a measurable delay (5 to 7 minutes) on thirst. If true polyuria is not present pituitary posterior lobe extract is without noticeable influence on the thirst.

The fluid restriction test, with study of the urine specific gravity, provides a safe method of analysing the relative importance of polyuria and thirst, in any particular case.

The biochemical changes in the blood are not necessarily related to the endocrine disturbances, since the overload of water, such as occurs in voluntary polydipsias, induces hypoproteinæmia and loss of chlorides; the overload constitutes a reserve of water (from 700 to 300 c.c.). Similarly, the loss of water, after the restriction test must not be taken to indicate dehydration since it frequently represents the removal of the water put aside during the excessive intake of fluids.

It was recently demonstrated that infiltration of the stellate ganglia with novocain induces a transient secretion of saliva in patients with diabetes insipidus as well as in those with polydipsic polyuria. This points to thirst being due to a reflex inhibition of the secretion of the saliva in the different types of diabetes insipidus.

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Dr. O. Garrod and Dr. J. E. Cates: *The Effect of Intravenous Nicotine on Urine Flow in Diabetes Insipidus*

As the antidiuretic action of nicotine had been attributed to the liberation of antidiuretic hormone (Burn *et al.*, 1945), the effect of the pure alkaloid was studied in diabetes insipidus. There were 12 subjects of whom 2 were normal, 2 had functional polydipsia and 8 had diabetes insipidus. The diagnosis of diabetes insipidus rested on the associated clinical findings, a fluid deprivation test and the hypertonic saline test of Carter and Robbins (Carter *et al.*, 1947).

Previous work had shown the amount of nicotine needed to induce antidiuresis to be 1 mg. in non-smokers and 2 mg. to 3 mg. in smokers (Walker, 1949). This was confirmed in the 2 normal subjects and in the 2 patients with functional polydipsia. These doses had little or no effect on urinary flow in the 8 patients with diabetes insipidus. However, twice these amounts (2 mg. to non-smokers and 6 mg. to smokers) caused a variable and sometimes marked antidiuresis in 5 of the 7 patients with diabetes insipidus to whom these doses were given. The side-effects were

severe, but changes in glomerular filtration rate did not account for the antidiuresis and a rise in urinary chloride concentration indicated some response of the posterior lobe of the pituitary gland.

The results were interpreted as confirming that the antidiuretic action of nicotine is due to the liberation of antidiuretic hormone by the posterior lobe of the pituitary and as indicating that in clinical diabetes insipidus the destruction of the supra-optico-hypophyseal system is often incomplete.

(A full account of these experiments, with case histories, is awaiting publication in *Clinical Science*.)

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Dr. A. A. G. Lewis and Dr. T. M. Chalmers: *Nicotine in the Diagnosis of Diabetes Insipidus.* [*Abstract*]

Nicotine, when given either by inhalation or by intravenous infusion, inhibits a water diuresis, causing a rise in urinary chloride concentration. This response is independent of glomerular filtration changes, as measured by inulin clearance, and is therefore considered to be due to the release of antidiuretic hormone.

There is a linear relationship between the durations of the inhibitions produced by graded intravenous doses of pitressin and the log dose. The response to nicotine can therefore be calibrated in terms of pitressin in a particular case. Study of 21 normal subjects showed that the inhalation of cigarette smoke until severe malaise results, releases an amount of antidiuretic hormone (ADH) equivalent to more than 100 mU of pitressin. This test was applied to 10 cases of diabetes insipidus. In 6 the release was less than 10 mU, while in 4 it was at least 100 mU. It is suggested that factors other than the destruction of the supra-optico-hypophyseal system were responsible for the polyuria in the last four cases.

[A report of this investigation is awaiting publication in *Clinical Science*].

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Section of Pathology

President—Professor R. W. SCARFF, M.B., F.R.S.Ed.

[*March* 21, 1950]

William Henry Welch
April 8, 1850, to April 30, 1934

By W. R. BETT

I FIRST met Dr. Welch in my salad days, when I was very young and very impressionable. Perhaps that explains why I continue to regard him as the most stimulating and the most charming person I have ever known. I am grateful to this Section for giving me the opportunity of paying my tribute, however brief, however inadequate, to his memory in the centennial year of his birth.

One of the most versatile men of his generation, William Henry Welch has been acclaimed as the Dean of American Pathology. Had he done nothing more than to enrich medical science with his researches in pathology and in bacteriology, Fame would not have passed him by.

Born in Norfolk, Connecticut, on April 8, 1850, of four generations of Connecticut doctors, Welch obtained his arts degree at Yale University, with high honours in Greek and Latin, and his medical doctorate at Columbia University, New York. After graduating he spent a considerable time in Europe, where he sat at the feet of some of the greatest men of the day. At Strasburg he studied histology under Waldeyer, attended the demonstrations of von Recklinghausen, and worked with the physiological chemist Hoppe-Seyler. At Leipzig he studied physiology under Carl Ludwig, and then joined the band of promising young men who had been attracted to Breslau by the fame of Julius Friedrich Cohnheim. Among these were Paul Ehrlich, Carl Weigert, and Albert Neisser. On his way home Welch stopped in Paris, where he heard the pathologist Louis Antoine Ranvier lecture, and in London where he listened to Joseph Lister.

Having established at Bellevue Hospital in New York City the first pathological laboratory in the United States, with characteristic energy he began the task, which may be said to be his greatest achievement, of introducing the scientific method into American medicine.

In 1879 he was appointed Professor of Pathological Anatomy and General Pathology at University and Bellevue Hospital Medical College, and four years later he accepted an invitation to become Professor of Pathology at the newly founded Johns Hopkins University in Baltimore. Before taking up this post he visited Europe again in 1884, athirst for knowledge of the new bacteriology. He was privileged to work with the great Robert Koch in Berlin, and ever after his interest in bacteriology equalled, if it did not exceed, his interest in pathology.

Harley Williams (1949) has aptly written of Welch that "In outlook and temperament, he remained European . . . yet his mind was truly American in its unconventionality and readiness to experiment".

The Pathologist

Welch's most original contributions to pathology include his work on acute œdema of the lungs, on venous thrombosis in heart disease—so eagerly and so quickly embraced by the clinician—and on diphtheria antitoxin. The *Bacillus cërogenes capsulatus* which he discovered in 1892, is to this day universally known as *Welch's bacillus*. In the same year he isolated the *Staphylococcus epidermidis albus*, describing its relation to wound infection.

One of his most brilliant and most original articles in the literature of pathology, "Adaptation in Pathological Processes", was first published in the *Transactions of the Congress of American Physicians and Surgeons* (1897, **4**, 284–310). It was reprinted in 1937 by the Johns Hopkins Press in its series of modern medical classics ("Bibliotheca Medica Americana"), with a notable introduction from the pen of Dr. Simon Flexner.

The architect of Johns Hopkins' greatness, Welch for several years was Dean of the Medical School. With John Shaw Billings he shares the credit for securing the appointments of many brilliant young men as professors. His suggestion that Osler and William Stewart Halsted should be chosen was eloquent of his enlightened views on medical education. Like Osler, he had returned from Europe with the firm resolve to see in the United States properly organized institutions devoted to medical education and research, for as a student he had listened for hours every day to the didactic, stereotyped lectures which were so characteristic of the medical schools at that time. As Osler fought for teaching by the bedside, so Welch sought to establish laboratories in which students might learn by investigation and research. As a teacher Welch had the satisfaction of seeing many of his former pupils occupying chairs of pathology in American universities; one, George Henry Falkiner Nuttall, became Professor of Biology at Cambridge and founded the *Journal of Hygiene*.

During the whole time that Welch was Professor of Pathology at Johns Hopkins University (1884–1916) he was also pathologist to the Hospital. Describing his methods in the laboratory, Dr. Simon Flexner (1941) wrote: "Welch's system was particularly productive because of the wide range of his interests. In each of the German laboratories where he had worked, one speciality had been taught, but Welch combined the Virchowian pathology of von Recklinghausen with the experimental pathology of Cohnheim, and added to them the bacteriology of Koch, creating a combination that existed perhaps nowhere else in the world in the laboratory of one man."

One of the founders of the Rockefeller Institute for Medical Research, Welch was chairman of its Board of Scientific Directors until the time of his death.

Public Health

From pathology and bacteriology this versatile and ever restless man transferred his boundless energies and enthusiasms to hygiene and public health, when in 1917 he assumed the directorship of the new School of Hygiene and Public Health at Johns Hopkins University.

During the first World War he was frequently consulted on questions of military hygiene, and at its conclusion the League of Nations readily availed itself of his wide knowledge of public health.

He presided over the Maryland State Board of Health from 1898 to 1922, and Baltimore in particular owes the modernization of its sanitation to his influence. The formation of the Yellow Fever Commission which was responsible for incriminating the mosquito in the spread of that disease, was due largely to his advice.



FIG. 1.—Drawing by Max Brödel, reproduced from menu card of Dinner in honour of William H. Welch, Baltimore, April 2, 1910.

The Medical Historian

The year 1926 witnessed yet another change in Welch's interests when he entered the relatively untilled field of medical history. At the age of 76 he was appointed the first Professor of the History of Medicine at Johns Hopkins, and he created a magnificent Institute which has become the centre of medico-historical activities in the United States. It is amusing to recall the pious hope cherished by his friends that the old man would regard his new post as an "easy chair" in which he could spend his last years in a leisurely study of his beloved books. Welch was well aware of this, but had no intention of regarding the professorship as a substitute for retirement. Without loss of time he went abroad to study library methods in the great European institutions and to buy books for the *William H. Welch Medical Library*, as it was designated at the official dedication ceremony.

Welch died of carcinoma of the prostate on April 30, 1934, in his own hospital.

Welch the Man

Let us try and recall the man as his generation knew him. Small, rotund, bald-headed, with a neatly trimmed Vandyke beard and mischievous, twinkling eyes, "Popsy" Welch was a confirmed bachelor, who lived and moved in an atmosphere of mystery. Though officially he occupied two small rooms crowded with books, he never appeared to be in Baltimore. He was supposed to take his meals at his Club, when he was in town, but he was always in New York or abroad—or so it seemed. Possessed of fabulous, almost uncanny memory, he knew the answer to everything without even pretending to work. Always busy, always having far too many projects on hand, he was usually late for his lectures, and it was said of him that he would start lecturing while still climbing the stairs to the theatre. At times his students did not understand a word of what he was trying so eloquently to tell them of the new pathology, but at other times he succeeded admirably in coming down to their level.

As an editor he was far from ideal. Though trained in Germany, he was a most untidy person who hardly ever answered a letter. Correspondence and manuscripts accumulated on his desk, and when the mountain became unmanageable, he proceeded to spread a newspaper on its summit and began a second storey. He loved food, cigars, and conversation. Of conversation he had made a fine art: he would talk on and on—literally for hours, and men would listen to him entranced, for to them it seemed that there was nothing he did not know in this world.

But perhaps the most vivid recollection some people retain and cherish of this remarkable and lovable man is seeing him strolling along the boardwalk at Atlantic City, his portly figure inadequately attired in the scantiest of one-piece bathing costumes—rubbing shoulders with the crowd, delightedly watching the children all sticky with Eskimo pie, amusedly contemplating the antics of harassed fathers trying to retrieve their lost flock.

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United Services Section

President—Sir HENRY TIDY, K.B.E., M.A., M.D., F.R.C.P.

[*March* 2, 1950]

Some Aspects of Atomic Medicine

By Surgeon Commander J. M. HOLFORD, R.N.

PART of the duties of Service medical officers is to form a considered judgment of the various hazards to which Service personnel are likely to be exposed. The object of this paper is to draw attention to some of the factors which are relevant to this task in connexion with the atomic bomb.

Atomic explosions, like chemical ones, produce most of their effects by heat and blast. These are no novelties in military medicine and there is ample past experience to draw on in estimating their magnitude. Ionizing radiations, however, are newcomers to the military field, and it is to their effects that civilian and military speculation has mainly been directed.

The principal ionizing radiations known are α, β, and γ rays, X-rays, and neutrons. All are capable of producing the same effects on living cells, though their relative efficiency varies. The variation appears to be due to the different ways in which the ions are distributed in the cell. They all have one feature in common, however. Only about one-third of the total ionization is produced by the primary particle or radiation quantum. The remaining two-thirds are caused by electrons set in motion by the primary particle (Gray, 1947).

Work on the irradiation of aqueous solutions throws some light on the mechanism by which damage to living cells may be caused (Allsopp, 1947; Lea 1947; Dale, 1947). It seems that free hydrogen and hydroxyl radicles can be produced in water and, particularly in the presence of dissolved oxygen, hydrogen peroxide can be formed. Protein molecules are susceptible of attack by the highly reactive free radicles. In addition, large protein molecules offer direct targets to ionizing particles and may suffer disruption by a hit on one of their constituent atoms. Dale (1947) has shown these effects on an enzyme, crystalline carboxypeptidase, in solution. It is probably fair to say that despite a large amount of radiochemical research it is still not certain whether direct or indirect action plays the greater part in the effect on living cells. It seems clear, however, that enzyme inactivation and nucleoprotein changes are

the main biochemical lesions. Using ultraviolet absorption as an indicator Mitchell (1943) observed changes in the nucleoproteins before morphological cell damage appeared.

Morphological changes in cells have been studied by the usual histological methods. The primary change occurs in the nucleus and is commonly a coagulation of the chromatin: pyknosis. This is followed by karyorrhexis: the disintegration of the nucleus and distribution of chromatin material throughout the cytoplasm. Finally, liquefaction of the whole cell mass occurs. An interesting study on irradiation of plant cells with α particles has recently been reported by Gierlach and Krebs (1949). The vital stain fluorochrome-acridine-orange was used. This stain is taken up by living cells without apparent disturbance of function, staining the cytoplasm pale pink and the nuclei green. On death of the cell the nucleus stains red. Thin strips of tissue were watched under α bombardment from polonium deposited on nickel foil: α emission is a random phenomenon and the statistical distribution of the affected cells could be clearly seen.

Not all cells are equally vulnerable to radiation. The mitotic process is especially sensitive. Mitosis tends to be delayed and, owing to chromosome changes, cells which manage to survive in the resting phase often die when they attempt to divide. It follows therefore that tissues in which cells are undergoing rapid division are, on the whole, the most affected. As long ago as 1906 the law of Bergonié and Tribondeau was formulated, stating that the radiosensitivity of a tissue is proportional to its reproductive capacity and inversely proportional to its degree of differentiation. Metabolic activity is another factor which must be taken into account. Increased activity brings increased sensitivity. In terms of human tissues this means that the order of vulnerability, starting from the weakest, is: lymphocytes, granulocytes, epithelial cells, endothelial cells, and connective tissue. Muscle, bone, and nerve cells are all highly resistant.

From a detailed consideration of the known facts of radiochemistry and radiobiology it would be possible to deduce with reasonable accuracy the clinical picture of acute radiation illness in man. The clinical response to acute whole body radiation is, as it were, the algebraic sum of the various biochemical and tissue effects and the body's adaptive response. For example, generalized protein denaturation produces histamine-like substances, which in their turn cause increase of capillary permeability. Direct depression of hæmopoietic tissues and of the adrenal cortex show themselves in much the same way whatever the primary cause. The latent period is a manifestation of the effect on mitosis. The injured cells manage to function, albeit a trifle lamely, until division. Large numbers then die and symptoms appear. It is not intended here to enter into any detailed discussion of the clinical aspects of acute radiation illness. Admirable accounts have already been published (Cronkite, 1949).

The published work on acute radiation illness deals in the main with the results of a single large exposure. In the Services there is naturally much interest in the effects of repeated or continuous exposure. It is easy to conceive that ground or materials may be contaminated with radioactive products and yet circumstances may make it vital that their use be not abandoned. Now, in general, particulate damage done by radiation is not reversible. Many radiochemical reactions are, of course, reversible in the chemical sense of the term, but from the biological viewpoint what happens is that the radiation dose leaves behind it a certain amount of completed irreversible chemical change, the amount depending on the efficiency of the reaction in the given circumstances. Looked at in this way, the effects of repeated dosage are simply additive, and the time taken to deliver the dose would not matter. However, the body

has powers of recovery and repair. Processes of detoxication and excretion, cell regeneration, and inflammatory repair are all called into play by the presence of radiation injury. When therefore dosage is spread out in time renewed injury and recovery are going on side by side, and the clinical result does not support the view that the effects of repeated doses are additive.

Fractionation of dose has been studied by radiotherapists over many years. A useful review has been published by Cohen (1949). He points out that completely irreversible reactions are covered by the Bunsen-Roscoe law.

$$I\ T = k$$

that is, the result is proportional to the product of intensity and time. Where the reaction is, in part, reversible or a uniform rate of recovery is going on at the same time the effect can be expressed by Swartzschild's law

$$I\ T^m = k$$

where m is a positive fraction. Radiation dosage is usually expressed as total dose rather than average intensity, so that taking $D = I \times T$ Swartzschild's equation becomes

$$D = k\ T^n \quad \text{where } n = 1 - m$$

This equation corresponds very well with clinical observations: n is known as the recovery exponent. It is different for different tissues. For normal skin a value of 0·30 has been found by several observers, whereas for squamous carcinoma it is about 0·22. This means that normal skin recovers rather more rapidly than squamous cancer, and this differential is the theoretical basis for fractional dosage in treatment.

What is required is a general recovery exponent which will give some idea of the efficiency of repeated doses in producing acute illness and death. Material collected by J. S. Mitchell (unpublished) is consistent with an exponent of 0·36, though Mitchell himself prefers not to use equations of this type in interpreting his results. He has further found that the doses of X and γ-radiation which produce skin and tumour reactions under the different conditions of both fractionated and continuous irradiation commonly used in radiotherapy can be explained quantitatively in terms of the theory of 2-hit chromosome interchanges, with the inclusion of a small linear term. It is emphasized that this numerical agreement does not necessarily imply the correctness of the suggested mechanism of radiation action.

Swartzschild's equation would read therefore

$$D = k\ T^{0.36}$$

Taking $D = d\ T$, where d = dose per day and T = number of days exposure, this can be transformed to

$$k = d\ T^{0.64}$$

The quantity k is now the dose which, if given in one exposure, has the same acute effect as a dose d given daily for T days. Thus if, for instance, 16r is given on each two successive days, or 9r daily for five days, in each case the acute effect is the same as if 25r were given in a single dose. Clearly, the equation could not be expected to be valid for periods longer than a few weeks, as chronic effects from repeated small doses would begin to dominate the clinical picture. However, it probably has a genuine statistical value. If the percentage of casualties to be expected from exposing a group of men to a given instantaneous dose is known, a similar result will be likely if the dose is fractionated in accordance with the equation.

An aspect of radiation exposure which has caused a certain amount of apprehension is the question of genetic and gonadal changes. These changes are mediated by damage to chromosomes. There are two principal effects. Firstly, a hit on a gene may cause a mutation which is probably a molecular isomerization in the gene. Secondly, chromosomes may suffer fracture or other mechanical damage It is known that either of these events may be produced by a single hit by an ionizing particle. The amount of damage so done is additive; that is, it depends solely on the total dose and not on its distribution in time.

Multiple chromosome fractures have been extensively studied (Catcheside, 1947). Fragments of chromosomes which are separated from their centromeres are liable to be lost altogether at mitosis. If the fragments are of appreciable size the newly divided cells will be non-viable. On the other hand, reunion of fractures often takes place, but with the wrong pieces. Thus chromosomes with two centromeres may be formed. Such chromosomes make a chromatin bridge between the daughter cells at mitosis. This is a mechanical obstacle to the completion of the process and as a rule both cells die. Some types of chromosome translocation are viable but give rise to hereditary abnormality.

The general effects of radiation on mammalian testes have been reviewed by Glücksmann (1947). As far as viability is concerned, the more primitive the cell in the spermatogenic tree the more sensitive it is. Nevertheless the dose required to cause permanent sterility is large, and if delivered as whole-body radiation would be lethal. The cycle of events when a moderate recoverable dose is received is broadly as follows. Spermatogenesis is much depressed, but the mature sperms do not die in great numbers. They do, however, suffer chromosome breakages and mutations. Human sperms stored in the epididymis remain fertile for about twenty-one days and motile for about forty-two days. This means that for nearly a month after exposure fertile mating is possible. Many of the mature sperms are now carrying dominant lethals, which means that any resulting zygote is incapable of full development and will either fail to implant in the uterus or will abort at some stage. There is a theoretical possibility that a grossly abnormal embryo might be brought to full term. If the sperm is carrying only a gene mutation and not a gross chromosome disturbance the mutation will almost certainly be recessive and will not interfere with the development of the embryo. Unless it is sex-linked, when it would appear in half the males of the next generation, it will have to wait for a suitable partner in subsequent matings before it can become manifest.

After the mature sperms have been used up a period of total or partial sterility will follow while the spermatogonia regenerate. The distribution of abnormality in the new race of sperms will be different. The dominant lethals will have vanished. Mature sperms can carry them because they have no more dividing to do, but such gross chromosome changes are fatal at mitosis and so are eliminated in the maturation divisions. This process is known as germinal selection. Recessive mutations which occurred in the spermatogonia are not so eliminated, and there are also some viable chromosome rearrangements which may get through. In the case of fractionated doses these various effects are all going on side by side. The final result, when all dosage has ceased, is a reduction in sperm count, usually small, which may, however, persist almost indefinitely, and a permanent increase in the percentage of sperms carrying mutations.

A particular viable chromosome rearrangement which might be of importance if a large population is irradiated is that which gives rise to hereditary partial sterility. This has been extensively studied in mice by Snell (1941) and others. As it is due to a very common type of chromosome disturbance there seems little reason to doubt that it could occur in man. The diagram represents two autosomal chromosomes in

a gamete after the reduction division. In an irradiated gamete of the opposite sex these two have suffered fracture and the wrong ends have joined up causing an interchange of chromatin.



After fertilization the zygote has its full complement of chromatin and can develop normally. But when it grows up and produces gametes of its own a new effect appears. At meiotic first prophase the four chromosomes are arranged thus:



At the reduction division these have to separate into two pairs, one pair going to each gamete. If they separate at random there are six possibilities, but only four are likely. In mice it has been shown that these four occur with nearly equal frequency. They are:



The latter two pairs have a duplication deficiency and produce a non-viable zygote. Thus half the matings are infertile. The other two are fertile, but one perpetuates the abnormality to the next generation and so on indefinitely. Half the living children in each generation have half the normal fertility. Experimentally in mice the strains appear to have started from irradiated mature gametes, but it is not theoretically impossible for the initial change to occur in a spermatogonium.

It remains to be considered what are the social effects of these possibilities and how far Service medical officers should give any weight to them. There is a tendency at present to play down their importance. It is pointed out that the chance of spontaneous mutation in a single gene is only about 1×10^{-5}. As human genes number some 5×10^3 that means that about 5% of sperms carry mutations. It is calculated that a dose of 50r will double this rate, and as the effect is in the spermatogonia the doubling is permanent. Even so, admitting the fact that nearly all the mutations are deleterious, they are practically all recessive. Their spread is slow and they will need several generations before they are likely to meet another recessive partner and manifest themselves. With regard to the reduction in sperm count, that is small and, it is said, unlikely to affect fertility greatly. The possibility of hereditary partial sterility in man does not seem to be discussed in the literature at all.

It seems to the writer that there is a case for taking these dangers slightly more seriously. It may be over-optimistic to assume that reduction in fertility will be no more than parallel with the reduction in sperm count. In whole-body radiation it is not inconceivable that other features of the seminal fluid may be adversely affected. The question of hereditary partial sterility is still speculative. However, the net reproduction rate in England is not such as to allow us to regard even small and sporadic reductions in fertility with complacency.

The human race is already bearing a large burden of unfavourable recessive mutations. If the burden is progressively increased a stage will be reached when manifest recessive abnormalities will become much more frequent. No one would like to see such well-known recessives as Friedreich's ataxia or the muscular dystrophies on the increase. Furthermore, there are many common diseases with a family flavour about them of which the genetic basis has not yet been fully elucidated. One might instance diabetes mellitus, schizophrenia, the allergies, and some forms of malignant disease. It may be unwise to stir up our genes too much until more is known about them.

The addition which radiation dosage is destined to make to the mutation burden may be small, but it is significant because it is one of a number of tendencies all in the same unfavourable direction. In a less sheltered society harmful recessives tend to be weeded out by natural selection. We, on the other hand, make every effort to nourish them and allow them to breed. We are prepared to tackle the most unpromising human material, keep it alive at vast expense and with prodigious ingenuity, and hail the result as a triumph of medicine. Humanitarian considerations forbid us to act otherwise, but it must not be forgotten that every such triumph tends towards dilution of the breeding stock. As the custodians of biological knowledge in its application to human welfare the medical profession must have some responsibility in this matter, but very little thought seems so far to have been given to it.

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Group Captain G. H. Morley, R.A.F.: *Irradiation burns.*—There is no one specific treatment for all types of burns in all cases. The treatment of very large numbers of burn casualties, many complicated by associated injuries and possibly by irradiation, will occasion too severe demands on medical staff and equipment if the elaborate methods of the past and present are followed. In this connexion the success of Mr. A. B. Wallace of Edinburgh (Kyle and Wallace, 1950), in treating burns in children by exposure to air and penicillin dusting must be noted with great interest as one more method which seems fairly simple and indicative of a possible alternative line of treatment.

"Self help" by the population may be of great importance by increasing confidence and morale and by lessening the establishment of infection in burns and wounds before early treatment can be organized in a major catastrophe. One substance which may prove of value for issue to the individual as a first aid or self-help cream is dibromopropamidine, on which work has been published (Arden, 1949; Champion and McDowall, 1949) and is continuing.

There would undoubtedly be large demands for blood and plasma transfusions and the development of plasma substitutes such as "Dextran" must be followed with very great attention.

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Dr. J. F. Loutit: *Effects of ionizing radiation.*—I am sure that Surgeon Commander Holford was right to sound a note of caution in his discourse. In this connexion I should like to take up one of his points. He has adduced the formula $k = d\ T^{0 \cdot 64}$, equating the effects of multiple daily doses of radiation to those of a single massive dose. As this was derived from radiotherapy on man it is by far the best figure to take. On the other hand it was derived from localized irradiation and one wishes to use the figure for irradiation of the whole body. Here only the results of animal experiments are available. Under the auspices of the Manhattan District a number of such experiments were carried out in the United States a few years ago. From such of these experiments of which satisfactory protocols are available my colleague Dr. R. H. Mole has been able to show that the statistics of mortality are compatible with a hypothesis which presumes that the damage produced by a dose of radiation is initially proportional to the dose and thereafter *increases* exponentially.

$$D = de^{bt}$$

(where D = damage
d = dose of radiation
b = constant
t = time)

$$\text{The total damage on the } (n + 1)\text{th day} = \frac{de^{b}\,(e^{nb} - 1)}{(e^{b} - 1)}$$

The most important difference between this formula and that of Surgeon Commander Holford is that the latter postulated a continued recovery from damage, while this one predicts an increasing accumulation of damage. Apparently it reflects the really long-term effects of radiation on life-span, whereas the other indicates the more or less immediate clinical results.

Another quite different point deserves, I think, our consideration. If we consider the treatment of acute over-exposure to ionizing radiation, the one regimen that has won universal approval is blood transfusion. This is logical in so far as an acute hypoplasia of the bone-marrow is produced. It is notable, however, that there has been no adequate clinical trial: it was not possible at Hiroshima and Nagasaki. Furthermore, there has been no controlled experiment with animals to prove its value. When the subject is considered dispassionately, one cannot expect the transfusion of whole blood to be effective in the dangerous stage of more or less complete absence of leukocytes. Many litres of fresh whole blood would be required daily for each case to maintain an adequate level of circulating leukocytes: the life of the leukocytes in the blood is only of the order of a few hours to a few days. Therefore, concentrated material like leukocyte cream would theoretically be required, but the mechanical and chemical damage to the leukocytes, attendant on the preparation of such cream, might invalidate its use. On the other hand one would expect transfusion of stored blood to be most effective as replacement-therapy when red cells, lost in bulk during hæmorrhagic periods, cannot be replaced by the hypoplastic marrow. It is in such cases that one might expect blood transfusion to be life-saving.

[*June* 1, 1950]

DISCUSSION ON PSYCHOLOGICAL SELECTION OF COMMISSIONED OFFICERS AND OTHER RANKS

Dr. J. B. Parry (Senior Psychologist to the Air Ministry): *Selection of Aircrew.*

First a word about selection generally. All through history persons have somehow been assigned to different lines of occupation, some getting the jobs they are interested in, others being less successful. To get a quick perspective on the main issue on the problem of selection it may be helpful to consider three possible approaches to the task of relating men to jobs. The first of these approaches I will call the method of nomination. The chief point to be noticed here is that in assigning a person to an occupation remarkably little attention is paid to his individual capacities; the emphasis is much more on his background, that is to say his family, his friends or possibly the reputation of some benefactor who is anxious to advance him. This approach is comparatively unusual to-day, but it should be realized that up to a hundred years ago almost all positions came to be occupied in this way. Then about the middle of the last century came the second phase in which a serious effort was made to measure all candidates for certain positions against some common standard. This objective

is exactly the same as the objective of selectors to-day; what marks off the second and third approaches is the instrument they adopt, not the goal they set out to achieve. The instruments that came into wider use a hundred years ago were the essay type examination as a gauge of ability and the unstandardized interview as a means of appraising personality. In this Discussion we shall see a shift-over to the use of the objective test (as a measure of abilities and skills) and to deeper and more controlled ways of appraising personality.

In 1939 aircrew selection was conducted almost exclusively by means of the unstandardized interview. This should not have been necessary as in the last half of the First World War a considerable amount of work had been done in various countries to establish a sound selection technique, but unfortunately all these efforts were laid to rest after the Armistice, with the result that every English speaking air force, except the U.S. Naval Service, had to start afresh ten years ago.

It may be well to state briefly the objections to what has been termed the unstandardized interview. There are four main objections, two referring to the choice of interviewers, the other two to the methods they are required to follow. To begin with there is the assumption that any reasonably able person can conduct a good interview, or in other words that interviewing calls for no particular skill. Very brief reflection will, however, show that good interviewing demands at least two skills, first the ability to maintain an easy conversation even in the face of an unco-operative partner, and secondly the ability to interpret correctly what comes out of that conversation. There is not the slightest reason that I can see to assume because a person has been, say, a good pilot that he can automatically do either or both of these things. I have been concerned in the last few years with the training of many hundreds of interviewers and all the evidence goes to show that about one person in ten, however competent in other directions, is incapable of learning to interview well. The second fallacy is that those who have a latent capacity for interviewing do not need to have it brought out by training. The evidence is that short training courses invariably help not merely those who find interviewing difficult but those who have an undoubted flair for it. By this means it is possible both to detect those wholly lacking in capacity, and for those who are potentially good, to remove in days faults that might otherwise have dogged them for years. Thirdly it used to be assumed that there was no need to supply interviewers with any analysis of the qualities they were required to look for, that is to say it was taken for granted that the possession of pilot qualities would stand out a mile and that the lack of them would be equally apparent. This would not have been true even if only one quality had been desirable, but a pilot's task being a highly complex one the assumption was even less justified. And then lastly the need for any interviewing aids, whether in the form of test scores or rating scales, was completely overlooked.

There is no time to trace in detail the evolution in aircrew selection methods during the last ten years. Instead I propose to consider the different reasons for which aircrew are failed in their training and then to see what provisions are made in the selection programme to anticipate failures of each kind. With the pilot there are three clear reasons for failure: failure in ground subjects, failure in personal qualities, and, of course, failure to learn to control a machine in the air. These reasons are factually as well as logically distinct, that is to say it is comparatively unusual to find a person who fails in all three or even in more than one. The existence of three comparatively unrelated factors, each essential for success in training, obviously narrows the field for selection considerably. The case is not quite so extreme with the other aircrew categories although there too there is usually some sort of conflict between the possession of the necessary personal qualities and the possession of specialized abilities.

To avert failure in ground subjects several early steps are taken. First of all only persons of School Certificate standard are invited to apply for the higher aircrew categories: as, however, there are many who have been denied the chance of actually sitting for this examination it is impossible to restrict applications to those who are in possession of the Certificate. Secondly, a series of four written tests is administered at the Selection Centre to check up on the educational standards of those who present themselves; these tests measure respectively general intelligence, general science, elementary mathematics, and all-round educational knowledge. Thirdly, those who do rather poorly on the foregoing tests but who are satisfactory in other respects are interviewed by an Education Officer who is empowered to send them to a school of educational revision before they enter on aircrew training proper.

Whereas at one time the interviewers were expected to weigh up everything relative to aircrew success, to-day their task is restricted to the measurement of personality and temperament. During the last four years steps have been taken to ensure that the assessment of these qualities is firmer than it used to be. First the nature of the qualities deemed essential in the discharge of aircrew duties was determined by questionnaire methods. As a result of pooling the opinions of several hundred highly experienced aircrew officers it was found that a strong measure of agreement existed as to what was important and that, on the whole, traits easy of assessment were considered of relatively little moment. A trait is said to be easy of assessment when direct evidence of it is available to the interviewer; thus a man's bearing can be seen and his diction heard, but his initiative and power of decision can be neither heard nor seen. To build up a reliable interview technique for the assessment of a number of inferred qualities has proved a tricky business but definite progress has been made, first by briefing fully all who are to conduct the interviews; secondly by supplying them with a fully annotated rating scale, and finally by carrying out repeated statistical checks to ensure that each interviewer is conforming to a reasonable pattern in his assessments.

In the early months of the war interviewers were still expected to assess the skills required by pilots, navigators, and others. They did their best at an impossible job, but their best proved not to be good enough. Thus in 1941 it was found that a quarter of all pilot trainees were regularly failing to learn to fly while overall wastage was in the neighbourhood of 50%. Two possible ways of improving such a situation can be thought of and both have been tried. Originally it was decided to put pilot applicants through some controlled flying tests during the first twelve hours of dual instruction. This Work Sample method (known as Flight Testing or Grading) immediately reduced training wastage by about half; for obvious reasons, however, it had no effect on the training of the five remaining categories. The other method is by building up a battery of laboratory tests, some written, some practical, with a view to estimating on the ground the aptitudes required by the different categories. This method came into force in 1944[1] and is the one still used to-day. It has the merit of great flexibility and cheapness. All aircrew applicants are required to take the full battery of tests lasting 1½ days so that the ability of each in respect of all the categories may be accurately assessed. The three selection instruments just described, that is to say the intelligence and educational test battery, the interview, and the aptitude tests, all take place at the same Centre so that it is possible to relate their results before anybody is accepted or rejected.

So much for the programme to-day. It now remains to try and evaluate its contribution. There are two ways of approaching this, first by consideration of training wastage figures, and secondly by follow-up methods. When we are talking about

[1] A considerable debt is owed to the U.S.A.A.F. who generously made available numerous written tests.

training wastage there are several pitfalls to be avoided. We must not, for example, assume that because a wastage figure strikes us as high the selection situation is necessarily bad. If we do this we may be guilty of one or more of the following fallacies:

(i) We do not know what the wastage would have been if there had been no selection or a different kind of selection. If, for example, current methods are reducing failure from 50% to 25% they are obviously making a considerable contribution.

(ii) We must learn to distinguish predictable from unpredictable wastage. It is commonly taken for granted that all wastage is training failure but this is often very far from true. It is correct to regard as wastage people who withdraw from training for, say, compassionate reasons, but it is not correct to regard this as failure or to think of it as something that the selectors could possibly have foreseen. Wastage of this unpredictable kind can reach a high figure, sometimes more than half the total.

(iii) It may even happen that predictable wastage is high and the selection system good. If this sounds paradoxical it is because we tend to think too much in terms of abstract standards. In fact there is almost always a tension between the claims of quality and quantity. This can only be disregarded if the supply of high grade human material is considerable; where this is the case predictable wastage can be almost entirely avoided by good selection. Far more often, however, we are compelled to go further down the scale and in the interests of numbers to select from a class which we know will yield relatively high wastage.

Finally there is the test of validation. In 1944/5 I had validation studies carried out in respect of large samples of cadets entered for each of the six main aircrew categories. The end of the war and the large scale suspension of training interfered with this plan to some extent but nine studies were completed, two in respect of pilots, two for navigators, one for air bombers, three for flight engineers, and one for gunners. (In the case of wireless operators we ran our heads against a statistically unusable criterion.) The final correlation figures for all nine of these studies were statistically significant to a high degree, the figures being 0·47 for two pilot samples, 0·64 and 0·69 for navigators, 0·23 for air bombers, 0·50, 0·28 and 0·33 for engineers, and 0·41 for air gunners.[1] These figures are a long way short of perfection but all give evidence of important contributions. This, however, was five years ago and in the interval much has changed. Consequently in 1948 I decided on a re-validation of our procedures and this is still in progress. I am not in a position to quote correlations but I have had χ^2 tests of significance carried out in respect of the samples of pilots and navigators who have so far gone through training.

To summarize what has so far been found:

(1) Pilots who fail in their ground subjects tend to have very low scores on the battery of intelligence and educational tests.

(2) Pilots who cannot learn to fly appear three times as often in the lower half of the pilot aptitude test scores as in the upper half.

(3) Navigators who fail their ground subjects appear three times as often in the lowest third on their test scores as in the top two-thirds.

(4) Of the small number who have failed for lack of personal qualities none has been awarded the top three of the interview scores. (The range of interview scores for those accepted is only 6.)

[1]Where more than one figure is cited for a category, the second refers to the second phase of training; in the case of Flight Engineers it was possible to follow up all three phases. The sizes of the samples range from 900+ to 200+.

Dr. N. A. B. Wilson (Senior Psychologist to the Admiralty): *Selection of Naval Ratings.*

The wartime achievements of Service selection by psychological methods were considerable. Training failure rates were reduced to half or less of their former size; and many more men were enabled to go on courses for which they had at least some preference. This success was not achieved, as the cynic might suggest, because in the wartime Navy we had certain sanctions to hand. It was very largely possible because men were taken into their entry establishments *in large batches* for final categorization by teams of *skilled personnel selection officers.* This allowed us to fit individuals to their Service employments reasonably well while at the same time following an acceptable man-power policy; and second, it allowed us to concentrate selection skill where the crucial judgments were being made.

Circumstances have changed radically since the days of the " Hostilities Only " rating. With the defining of its post-war personnel policy the Royal Navy has decided to concentrate by far the greater part of its effort upon a comparatively small entry of regulars (i.e. men serving seven, twelve or more years) who can be given prolonged technical training and practice, many of whom will make the Navy their career. Men no longer enter in provisional categories which can be changed almost at will to meet manning needs or to satisfy the demands of efficient selection. Each man or boy negotiates his own choice of employment with the Recruiting Staff in one or other of some fifty recruiting centres. He is a volunteer for a specific category—Electrician, Stoker Mechanic, Seaman, Sick Berth Attendant, Stores Assistant, etc.—and his category cannot be compulsorily changed. If he fails in his technical training he may of course be re-allocated, but even then he has the alternative of leaving. The primary selection for the Navy to-day, then, is done in small numbers by Chief and Petty Officers and Commissioned Recruiters in recruiting offices all over the country. They are helped by two technical aids provided by my department at the Admiralty: a brief test battery and a short questionnaire which is filled up by applicants and checked by Recruiters. The aim of these aids is to elicit relevant facts to help the Recruiters in forming their judgments.

There are two very important exceptions to this system of general recruitment. Neither officer cadets nor artificer apprentices are selected through the ordinary recruiting procedure. Artificer apprentices, who provide nearly all the Navy's highly skilled tradesmen—electrical, air, engineroom, ordnance, and shipwright artificers—are selected by a procedure derived from wartime practice. Candidates who pass an educational qualifying examination are assembled in a Naval Establishment for two days at a time and are dealt with by a team consisting of one Medical Officer, five or six Personnel Selection Officers or Psychologists, and one Commissioned Recruiter. The procedure is comprehensive but the emphasis is upon aptitude assessment, i.e. assessment of suitability for and adaptability to a fairly rigorous engineering trade training and career.

To return to the general Naval entry: adult new entries are received weekly in six different establishments. Each youth or man goes through a new entry routine which involves an interview with a Personnel Selection Officer who has before him the Recruiting Centre questionnaire and results of further tests and questionnaires. The Personnel Selection Officer's survey is no longer as in wartime decisive, but is now confirmatory: or if he cannot conscientiously concur in the Recruiter's decision, he may suggest a change of category at the end of Part 1 new entry training. Personnel Selection Officers may recommend these changes and, if Commanding Officers concur, Commodores may allow them up to 15% of the entry. In fact, there is reluctance to change men once they have settled down and started, and before they have demonstrated their unsuitability by failing on a course; so the proportion of changes is well below the permitted 15%.

It will be seen that the functions of Personnel Selection Officers have changed somewhat since the days when they were selectors pure and simple. Their job is now:

(i) To advise on men who are seen to be badly misplaced either in their entry category or in the Service itself;

(ii) To make a first identification of men who may be worth watching as potential officers or higher technicians;

(iii) To fulfil a "welfare" function by causing each man to feel that his Service career is being expertly considered, in which process his own views are given considerable weight;

(iv) To form a cadre which could be at once expanded in an emergency; and

(v) To provide data for research designed to improve personnel selection, or to assist in the solution of man-power problems, or even to investigate basic psychological or sociological questions.

The Naval authorities take the common-sense view, that advancement *within* the Service should depend upon record, report, and the result of professional examinations. Therefore personnel selection is mainly a matter of providing appropriate filters at the entry stages. Many—perhaps most—ratings do not encounter " personnel selection " after that stage. If they do, it will most probably be when they go before an officer selection board. But we do have a concern in several specialization problems. We are minority members, for example, of the board which deals with the specialization of Naval Air Maintenance ratings into such groups as Mechanic, Safety Equipment Worker, Photographer, &c. We have also provided specialized test batteries to help with the division of anti-submarine ratings into Asdic operators, mine and weapon ratings; and also to help with selection of communications ratings who are chosen from among the Boy Seamen. The principal constituent of the last test is an adaptation of the American Speed of Response Test (for Morse aptitude).

The instruments of selection used are mostly conventional ones. *Information* about employment is provided, so that men may have a chance to express aspirations and make choices in an enlightened manner. *Biographical inventories* are completed by the candidates and annotated by Recruiters and Personnel Selection Officers. Except in the case of Boy entries, a " *personal inventory* " of a mildly psychiatric kind is also employed—mainly to locate men who may profitably be considered for psychiatric referral. The standard *test batteries* consist of an intelligence test of the Shipley Abstraction variety, a mechanical information test, a space perception test, and an arithmetic and mathematics attainment test. Finally, all the information available is focused in an *interview* between the candidate and the selector, and an attempt is made to co-ordinate all relevant considerations towards a satisfactory decision.

Since the Naval population has changed from " Hostilities Only " and " National Service " men to " Regular Engagement " men and boys, and since the outlook has changed from " What can we learn from the war? " to " How can we prepare for the future ? " much of the research validation has been taken almost overnight from our instruments and the work they do. We are, at present, in an interim position, doing personnel selection on the basis of research into the problems of an earlier population in a different situation. Much of it is obviously applicable, of course, but it is an urgent task to repeat and extend our research with our present population of career sailors. We have not been quite inert in this respect, although there have been difficulties. We are trying to take a longer view than would be possible in war, by giving some of the attention they deserve to problems of criteria for validation—the reliability of criteria, their structure as revealed by factor analysis, and the adequacy of partial or proximate criteria as substitutes for relatively inaccessible but obviously valid criteria.

Naval selection has been guided very largely by a team taken over by the Admiralty from the National Institute of Industrial Psychology in the early days of the recent war. The attitudes of the members of the team have been remarkably homogeneous. They may perhaps best be characterized by the following set of simple propositions:

(i) The co-operation of the candidates in selection is essential. To this end they must always be given relevant information. If so, they will to a considerable extent select themselves.

(ii) The interview must for long remain the central selection technique, even if it adds little or nothing to the validity coefficient of objective selection instruments. It is unparalleled for acceptability, flexibility, speed, and inclusiveness.

(iii) The best basis for the interview is a biographical questionnaire in which the candidate gives information about his initial opportunities, schooling, work record, technical and other interests and achievements, his part in community and leadership activities, and any special qualifications.

(iv) Simple, comprehensive, cumulative documentation of each man's career is often of far more value than any amount of testing. This carries the implication that staff must be capable of using records expertly.

(v) In a large-scale classification programme, such as the Navy had to undertake in the recent war, specialized tests, particularly if they involve apparatus or complicated scoring, are of limited importance. The demands of training programmes give a tremendous primacy to *general* ability, or rather *educ*ability; and a general classification test—if soundly constructed and simple to use—will do a remarkable proportion of the work which can be done by testing.

(vi) Interest and relevant previous experience can, where genuine, be even more important than intelligence. Tests of knowledge or trade experience to cover the main areas relevant to Service jobs are therefore exceedingly useful.

(vii) Educational status and educational proficiencies are at least as relevant to classification as the results of " pure " intelligence tests.

(viii) Finally, although personnel selection should be at the closest possible grips with its subject matter, its status should remain advisory, not executive. Technical selection methods improve, they do not replace, the usual Service procedures.

When I started, I remarked upon the comparative inefficiency of doing selection " in penny numbers " at scattered centres. In concluding, let me say that the trouble to which this at present necessary policy gives rise is not confined to difficulty in maintaining consistency of standards. Indeed our most notable difficulty has arisen out of a tactic designed to achieve consistency. This is a system of minimum scores on the general classification test battery, one for each recruitment category, which should—in theory, at least—ensure that the recruit is intellectually up to the requirements of elementary training in the category in which he has entered. Now as far as the elementary training stage is concerned, this probably works well enough. But beyond it there are snags which we believe are only just beginning to declare themselves. They arise from two facts: (i) a general shortage of really high-grade recruits and (ii) a very human feeling on the part of individual selectors and others that a man should, if at all possible, go into the highest grade of category for which by test score he is eligible. To put it in a concrete, though over-simplified, manner, the tendency is to make all high scorers into Writers, all middle scorers into Electricians and all low scorers into Seamen, Royal Marines or Sick Berth Attendants. The event which we fear is that all the potential higher rates—because test score and petty officer potential *do* go together, however sceptical some may be on the point—may be segregated in one group of categories! The remedy is simple enough in

theory—it is to enter *in each category* not only men who can pass the elementary training hurdle but also a proportion of men who can get over the hurdles leading to higher advancement. This idea of entering a *range* of ability in each category—not merely saying " you are a volunteer for this category and you have reached the necessary minimum test score "—is extremely difficult to put across in practice.

It is with suchlike man-power problems arising out of selection work that we are mainly concerned at the moment. We have attacked them by attempting to calculate the yield of potential petty officer quality and quantity in each entry category, and to some extent in each specialization, by each half-year since the Royal Navy reverted after the war to entering men on regular engagements.

Colonel B. Ungerson, C.B.E. (lately Chief Psychologist, Directorate of Manpower Planning, War Office): *Selection of Army Officers.*

War Office Selection Boards were introduced during 1942, after some months of preliminary experiment. As a result of continuous research, minor modifications of their original procedure were made during the war, but the general principles remained unchanged until the end of the war. Since that time, the composition of the Selection board has been modified and at present comprises Military members only, with technical officers (psychologists and psychiatrists) available for training of Board members, advice and research only. This change was brought about for a variety of reasons, including the shortage of psychologists and psychiatrists in the Army. Although the Boards have now no technical members, the tests and their working are supervised by technical personnel, on the establishment of a central research and training centre. It is of interest in this connexion that the Navy, the R.A.F., and the British Civil Service, whose procedures are largely based upon the Army's selection methods, retain technical officers as working members of their Boards.

In view of these last facts, and in order that this account may be of the greatest possible interest to members, my description of War Office Selection Board procedures will be based upon the methods used during the war.

Each Board arrives at its conclusions only when its members have lived with the candidates for two and a half days and, during that time, subjected them to specially devised testing procedures. The Boards during the war were constituted as follows: President (Colonel), Deputy President (Lieut.-Colonel), Senior Military Testing Officer (Major), Military Testing Officer (Captain), Specialist Psychiatrist (Major or Captain), Psychologist (Captain or Lieut.), Sergeant Testers. The first four of these were always experienced regimental officers. The last three together formed what was known as the technical team, who carried out specific tests which, interpreted in conjunction with others of a more practical nature organized by the Military Testing Officers, gave an insight into the candidate's fitness or otherwise for leadership. The procedure was completed by an interview with the President and the candidate was assessed on the total result of the evidence. The Selection Boards were usually in country houses set in pleasing grounds and the candidates during their stay at the Boards were treated as officers, except that each was known only by a number in order to ensure anonymity.

On the first day each candidate completed questionnaires about himself and underwent four tests, two objective tests of intelligence and two for the assessment of temperamental characteristics. These latter were a Word Association test and a test known as Murray's Thematic Apperception test. It should be noted that the tests used for character assessment cannot be objectively marked by laymen, but require skilled interpretation by psychologists or psychiatrists.

The intelligence tests were conducted by Sergeant Testers and results classified into 10 groups covering the entire range of the Army's officer population. Candidates failing to reach the level of the average private soldier, that is having lower intelligence than the men they would have to command, were almost inevitably eliminated, unless careful investigation showed them to possess compensating personality features.

Where the character assessment tests seemed to warrant it, candidates were interviewed by a specialist psychiatrist, whose task it was, helped by the results of the tests, to gauge not only the man's present state but its possibility of betterment under intensive training.

This testing and interviewing was essentially complementary to the practical tests carried out under the Military Testing Officers. The candidates were assembled into groups of eight and took part in various group activities. These included discussions, planning solutions to relatively simple practical problems, and a series of outdoor tests of a practical and non-military kind. Throughout all of these tests, the candidates' performance was under observation of the Military Testing Officers who made continuous records, not so much of the candidate's intelligence and planning ability, but of the personal interrelations of members of the group. This procedure was used because it was felt that personality could be judged only in dynamic situations in which personal relations were being built up among a group of human beings who had not previously met.

Many of the tests were deliberately framed in such a way that the group had no nominated leader and so that the group could be seen to evolve from a disorderly and unorganized condition into one of disciplined and organized efficiency. It was during this process that the most effective observations of the characteristics of the individuals could be made. The final step in selection was the Board Conference at which each member put forward his own conclusions about each candidate and an open discussion ensued. The various character traits of each candidate were recorded on a " profile " and the final judgment of the Board reached only after agreement on the rating to be accorded to each individual trait.

The most important characteristics of these Boards can be summed up as follows:

First they replaced the straightforward interview by a more complex and thorough procedure based upon scientific research.

Secondly, they employed mixed teams of soldiers, psychiatrists and psychologists.

Thirdly, it was always regarded as essential that the ultimate responsibility for officer selection rested with the military organisation rather than with its technical advisers; this meant that within the Board the President was responsible for co-ordinating the views of all members and for the final decision.

Let me now turn to the problem of research and validation. Considerable efforts were made during the war to validate War Office Selection Board procedures, but very grave difficulties arose in wartime conditions. Enough was done, however, to prove conclusively that these new Boards were more successful in forecasting success of officer cadets than had been the interview Boards which they replaced. Results of wartime research are to be published shortly under the auspices of the Medical Research Council, and I propose, therefore, to confine myself to a discussion of research since the end of the war.

The fundamental difficulty in validating War Office Selection Boards, as in validating any selection procedure, is to obtain a satisfactory criterion of success for those whom they select. Unless we have some reliable judgment of the success of a young officer, we are in no position to calculate how successfully a War Office Selection Board has carried out its work. After very careful consideration, we decided in 1946 to undertake a large-scale research programme, accepting as our criterion the gradings obtained by cadets at the end of their period at an Officer Cadet School. It was appreciated that this criterion was not necessarily reliable, and that it would

be a matter for further research to find out whether these gradings at the end of training correlated reasonably well with later performance in the field. In spite of the possible unreliability of these gradings, it was, nevertheless, decided that we should judge the success of War Office Selection Boards by the extent to which they succeeded in forecasting these training grades.

Using this criterion, we undertook a programme which can broadly be divided into four main steps.

First, we calculated the correlations between the grades allotted at all War Office Selection Boards on the one hand, and the grades allotted at all Officer Cadet Schools on the other. This gave us an over-all picture, and enabled us to judge whether the Boards were performing a useful function. We found that the correlation between selection and training was low, but was, nevertheless, significantly better than chance. We appreciated, of course, that this might be largely due to the unreliability of our criterion, and the results seemed sufficiently good to justify more detailed research, with a view to improving War Office Selection Board predictions.

We, therefore, passed on to the second stage, in which we calculated the correlations between single Boards and single Officer Cadet Schools. These calculations showed that there were very large differences between the forecasting efficiencies of different War Office Selection Boards, and also that we could forecast more efficiently for some Arms than for others. This was a promising result, since it suggested that our major task was to raise the efficiency of War Office Selection Boards to the level achieved by the best of them. Once this was decided, the next stage in our research programme became clear.

The third stage was a detailed study of the forecasting efficiency of individual Board members. We considered that if we calculated the correlations between the gradings allotted by individual Board members on the one hand, and the gradings obtained at the end of training on the other, we would obtain an objective indication of the efficiency of the individual assessors. This was a very laborious task, but its results were extremely interesting. We found that there were large differences in forecasting efficiency among individual assessors, not only at different Boards, but quite often when they were members of the same Board. For example, there was one case in which two Personnel Selection Officers with identical jobs at the same Board were so unequal in performance that one achieved a correlation of nearly 0·6 with O.C.S. gradings, while the other had a correlation which was not significantly different from zero.

Another interesting finding was that, although some psychologists and psychiatrists had thought otherwise, the differences in forecasting efficiency were just as great among the technical members of the Boards as among the Military members. In other words, it appeared that there were large individual differences, both among regular officers and among technicians in ability to spot the potential officer. From this finding, we argued that our next step was to study individual assessors from a psychological point of view, and this, the fourth stage in our research programme, is at present in hand.

The psychological study of individual Board members is no small task, since information can be collected only very slowly by highly skilled and psychologically trained observers. As the programme proceeds, however, we hope that we shall steadily increase our knowledge as to the most important characteristics making for success in the young officer. We shall also learn more about the selection and training of members of War Office Selection Boards. Progress will, undoubtedly, be slow, but the improvement of our techniques for assessing human character can hardly be expected to progress very rapidly. Those responsible for the methods of personnel selection in the Army would prefer to build slowly but stoutly upon the carefully controlled results of research rather than proceed more spectacularly but much less soundly by means of hunches and opinions.

Section of Radiology

President—S. COCHRANE SHANKS, M.D., F.R.C.P., F.F.R.

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The Treatment of Malignant Tumours of the Nasopharynx

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THE treatment of malignant tumours of the nasopharynx is of particular interest to the radiotherapist; as yet, radiotherapy alone offers a possibility of cure in malignant disease at this site.

This paper is based on a series of 54 cases treated at the Middlesex Hospital between 1935 and 1949. The number of cases is relatively small, and no detailed statistical analysis has been attempted.

INCIDENCE

Cancer of the nasopharynx is uncommon. In a recent paper Martin and Blady (1940) put the incidence at 2% of all malignant cases of the head and neck seen at the Memorial Hospital, New York. The Registrar-General's figures for 1948 show 55 deaths due to cancer of the nasopharynx out of a total of 79,537 deaths due to cancer, an incidence of 7 per 10,000.

A number of cases probably escape detection because the signs and symptoms are more often than not those of spread outside the nasopharynx, and a small silent growth, in a region difficult to examine, might well be overlooked.

Cancer of the nasopharynx occurs throughout the various age-groups, and not infrequently in young subjects; thus, in our series, 8 cases were aged 30 or under, and 21 cases (or 39%) were aged 45 or under. Men outnumbered women by 36 to 18, i.e. 2 : 1.

The age and sex incidence is shown in Table I.

TABLE I

Age-group	0–5	–10	–15	–20	–25	–30	–35	–40	–45	–50	–55	–60	–65	–70	–71
Male ..	—	—	—	1	1	1	2	1	7	4	3	7	6	3	—
Female ..	—	1	1	—	1	2	2	—	1	2	2	1	2	2	1
Total	—	1	1	1	2	3	4	1	8	6	5	8	8	5	1

DIAGNOSIS

The diagnostic problem presented by these cases is now well recognized. The initial symptoms may be classified under three headings.

Firstly, symptoms due to the presence of the tumour in the nasopharynx, such as nasal obstruction, by blocking of the posterior nares, deafness by blocking of the pharyngeal opening of the eustachian tubes, and nasal discharge and epistaxis due to ulceration and infection. These can be called rhino-otological symptoms. Epistaxis is often the first symptom in this group; direct questioning may reveal it to have occurred several months previously.

The second group is caused by extension of the growth beyond the confines of the nasopharynx. These tumours show a strong tendency to invade the base of the skull. This occurs either via the foramen lacerum, lying immediately above the fossa of Rosenmüller, which is often involved in growth early on, or occasionally the tumour invades through the body of the sphenoid. It is probable that some of these tumours start within the sphenoidal sinus and extend up into the skull and down into the nasopharynx at the same time.

Once inside the skull, the tumour spreads extradurally along the base of the brain causing paresis or paralysis of the cranial nerves in the middle fossa.

The most common neurological symptom is double vision due to paralysis of the external rectus muscle from involvement of the VI nerve.

Also commonly affected is the V nerve, producing pain and paræsthesia in its distribution, and weakness of the muscles of mastication if the motor root is involved. Less frequently the III and IV nerves are attacked, causing complete external ophthalmoplegia. Rarely, pressure on the ophthalmic veins may cause papillœdema.

The IX, X, XI and XII nerves are occasionally affected by intracranial spread, but they may also be involved extracranially in the region of the jugular foramen. Similarly, the third division of the V nerve may be involved in growth, as it passes close to the lateral wall of the nasopharynx after leaving the skull, as described by Trotter in 1911.

This symptom complex produces an extremely puzzling picture and the progressive nerve palsies may cause a mistaken diagnosis of cerebral tumour, particularly in those cases where papillœdema is present.

Fig. 1 shows a patient who complained of double vision and headaches in July 1946. He was investigated extensively as a brain tumour, including two ventriculograms, at another hospital. When referred to us in January 1947 he had a complete paralysis of the III, IV and VI nerves, and a partial paralysis of the V and XII nerves on the left, and a partial III, IV and V, and complete VI nerve paralysis on the right. Posterior rhinoscopy showed an ulcerated tumour in the left half of the nasopharynx.

Fig. 2 shows improvement of the ptosis two weeks after commencing deep X-ray therapy, and Fig. 3 shows his condition three years later. Unfortunately he has had a post-radiation endophthalmitis which has destroyed his left eye, but the nerve paralyses have completely cleared and he is apparently free from disease.

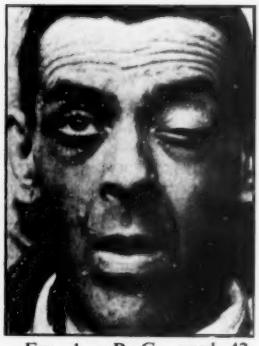


FIG. 1.—P. C., aged 42, before treatment, showing ptosis of left eye, and paresis of motor root of both fifth cranial nerves.



FIG. 2.—Same patient as Fig. 1, two weeks after starting deep X-ray therapy, commencing recovery of ptosis.

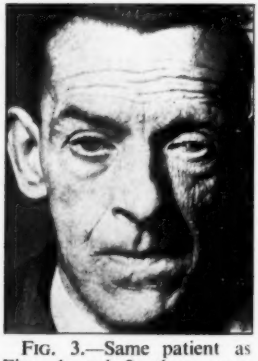


FIG. 3.—Same patient as Figs. 1 and 2, three years after treatment.

The third and most common way in which these cases present is with enlarged cervical lymph nodes. There are a number of cases where malignant glands in the neck are found, but in spite of careful search, no primary growth can be discovered. In the past these cases have occasionally been called primary malignant glands of the neck, but in a high proportion a nasopharyngeal growth is ultimately detected, though sometimes not until many months later.

In our series, 26 cases, that is just under a half, first complained of enlarged glands in the neck, and in 41 cases, or 76%, enlarged cervical glands were detected at the first examination. These were bilateral in 16 (30% of the whole group). 15 cases presented with oto-rhinological symptoms, and 13 cases with symptoms of cranial nerve involvement. This last group has been investigated to see whether it represents a separate entity, but it has been found that this is not so, apart from the symptomatology. Thus 7 of the 13 cases were transitional-cell carcinomata, but the other 6 presented a varied histology and the clinical course did not differ from that of other tumours within each pathological group. It is considered that invasion of the cranium depends on the site of the tumour within the nasopharynx rather than on its pathology.

When the type of initial symptoms is compared with the lapse of time before the first attendance in the radiotherapy department, it is interesting to note that of the cases with oto-rhinological symptoms none had complained for more than nine months, and one-half

for only four months. Whereas, when glandular enlargement or nerve lesions were the first complaint, some cases were not referred for up to two years, while only 50% were seen within nine months. This, I think, is an indication of the difficulty in early diagnosis.

Skiagrams of the nasopharyngeal region are most helpful in diagnosis. A lateral X-ray of the skull will often reveal a soft tissue shadow with partial obliteration of the naso-pharyngeal air space, while lateral tomograms may show this even more clearly. Fig. 4 shows such a tomogram cut before treatment, with total obliteration of the air space, and Fig. 5 shows the same cut after treatment, with re-establishment of the air space. A lateral



FIG. 4.—E. S., aged 60. Tomogram before treatment, showing obliteration of naso-pharyngeal air space.



FIG. 5.—Same patient as Fig. 4, similar tomogram after treatment.



FIG. 6.—Lateral X-ray of skull, showing gross erosion of pituitary fossa.

X-ray of the skull may show gross bony destruction (Fig. 6), but this is rare. Erosion at the base of the skull can be better detected by axial (submento-vertical) views, as shown in Fig. 7. Intracranial invasion and cranial nerve lesions may, of course, occur without evidence of bony erosion.



FIG. 7.—Submento-vertical view showing erosion of basal foramina on the left.

PATHOLOGY

Biopsy of the growth is most important both for histological verification and to determine treatment policy. It should be performed before treatment, as some of these growths are so radio-sensitive that histological recognition may be very difficult if appreciable treatment is given beforehand. In our series biopsy was performed in 52 out of 54 cases. In 47 cases it was positive, while no definite tumour was found in 5. In 43 cases, biopsies were obtained from the nasopharynx, and in 9 from cervical glands. These were usually cases where a cervical swelling had been excised prior to discovery of the primary.

The histological classification of tumours in this region is still not universally agreed. Debate has centred on the less well-differentiated epithelial tumours.

In 1921 both Regaud (as quoted by Reverchon and Coutard) and Schminke described the lympho-epithelioma: a tumour arising from epidermoid epithelium, intimately associated with lymphoid tissue. The tumours produced early lymph node metastases and were highly radio-sensitive.

Quick and Cutler in 1927 described a transitional-cell carcinoma in the pharynx, which greatly resembled the lympho-epithelioma but did not contain lymphoid tissue.

Much argument has ensued about these two tumours as many authors, amongst them Harvey, Dawson and Innes (1937) and Willis (1948) do not believe that they are separate entities. Godtfredsen (1944) classifies both lympho-epithelioma and transitional-cell carcinoma as sarcomata.

It would clarify matters if the tumours encountered were to be correlated with the normal structures present. Our histological classification is based on these considerations. Basically, two types of epithelium are found in the nasopharynx. Respiratory, i.e. pseudostratified columnar epithelium encountered in the anterior and upper part, and squamous epithelium in the posterior and lower part. The squamous epithelium overlying lymphoid tissue undergoes certain modifications, and can therefore be separately classified as lympho-epithelium (Jolly, 1911). There are numerous mucous glands and much lymphoid tissue; the latter is aggregated in three main masses—the pharyngeal and the two tubal tonsils. These masses tend to atrophy in adult life.

Malignant tumours can arise from any of these tissues. Thus, squamous epithelium gives rise to squamous-cell carcinoma, respiratory epithelium to transitional-cell carcinoma and lympho-epithelium to lympho-epithelioma. Unfortunately things are not always quite so simple, since respiratory epithelium tends to undergo metaplasia to squamous epithelium in old age and after minor trauma, and may then give rise to squamous-cell carcinoma, while, as will be explained later, transitional-cell carcinoma may also occur in squamous epithelium. Within the three groups there exist variations in the degree of differentiation, and the least differentiated type of each gives no indication of its parent epithelium, and thus a further group is observed, the undifferentiated carcinoma.

The mucous glands give rise to mucous gland tumours which, as a rule, are of low and local malignancy only, but do not respond well to treatment. The connective tissue elements form reticulum-cell sarcoma and lymphosarcoma and plasmocytoma.

The squamous-cell carcinomata vary in their degree of keratinization, and this can be made the basis of further subdivision, but I have grouped together tumours showing frank and early keratinization (Fig. 8), while including those with little or no keratinization in the undifferentiated carcinomata (Fig. 9).



FIG. 8.—(× 70.) Frankly keratinizing squamous-cell carcinoma showing well-marked epithelial pearl formation.

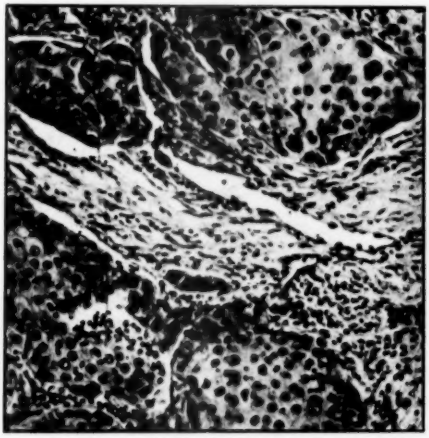


FIG. 9.—(× 100.) Undifferentiated carcinoma showing large pale clearly demarcated cells with no attempt at epithelium formation.

The transitional-cell carcinoma (Fig. 10) was described by Ewing (1940) as occurring in the nasal passages, the trachea, bladder and cervical canal. These structures are lined by stratified or pseudostratified cells which do not produce keratin, and do not become squamous except under pathological conditions, and carcinoma arising from this epithelium also fails to show squamous cells. In certain regions normally covered by squamous epithelium, such as the base of the tongue and the tonsil, a change may occur in the basal cells of the epithelium. They become more numerous and polychromatic, and carcinoma arising in this changed basal layer has no squamous character and is also classified by Ewing as transitional-cell carcinoma.

These tumours are not always easy to distinguish from the less well differentiated squamous-cell carcinoma, and in fact no such distinction is made by some authors. But in this series, transitional cell carcinomata form a very definite entity both as regards the clinical behaviour

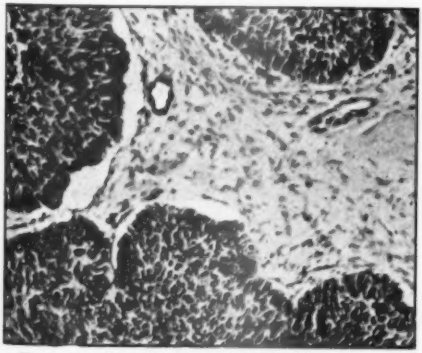


FIG. 10.—(× 70.) Transitional-cell carcinoma showing alveolar formation and broad epithelial columns.

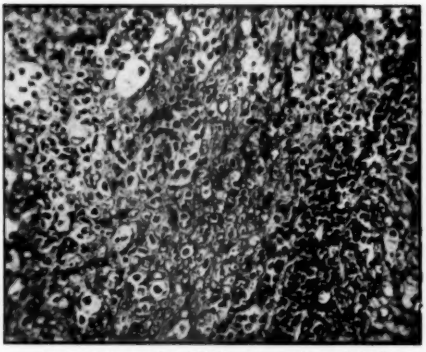


FIG. 11. — (× 150.) Lympho-epithelioma showing large palely staining cells with indistinct cell outlines in a lymphocytic stroma.

and prognosis. Thus 7 out of the 9 cases of transitional-cell carcinoma showed invasion of the skull, an incidence of 77% against 24% in the whole group, and cervical lymph glands were invaded in only 4 cases, that is 44% against 76% in the whole series.

A lympho-epithelioma is shown in Fig. 11.

The numerical distribution is given in Table II.

TABLE II

Carcinoma		
Squamous-cell	4	
Transitional-cell	9	
Lympho-epithelioma	9	
Non-keratinizing squamous and undifferentiated	19	
Mucous gland tumour	1	
		—42
Connective tissue tumours		
Reticulum-cell sarcoma	3	
Plasmocytoma	1	
Spindle cell sarcoma	1	
Lymphosarcoma	0	
		— 5
Indefinite histology	5	
		— 5
No histology	2	
		— 2
		54

It will be seen that carcinomata predominated greatly, and curiously enough no cases of lymphosarcoma were encountered.

Clinically, the undifferentiated carcinoma and the lympho-epithelioma bear great resemblance to each other in their growth-behaviour, early and extensive lymph-gland involvement, and response to radiation. In this again, these tumours are very much like most sarcomata in the nasopharynx.

On the other hand we have the keratinizing squamous-cell carcinoma, which is only moderately radio-sensitive, while the transitional-cell carcinoma, which usually responds well to radiotherapy, has a strong tendency to local recurrence.

TREATMENT

In all but 2 cases our treatment consisted of deep X-ray therapy. This was instituted along two different lines.

Firstly, in the radio-sensitive group where cervical metastases, often bilateral, were the rule, regional treatment was the method of choice—i.e. an area from the base of the skull



FIG. 12.—Large field treatment, the circle of light depicts the area treated.

down to the clavicle was irradiated *en bloc* by two large lateral fields. The portal used in an adult was a 20 cm. circle to each side of the head and neck (Fig. 12). The tumour dose given was 3,000 r–3,500 r in four to five weeks.

Because the large volume irradiated contains larynx and pharynx, the general reaction is usually marked, and careful nursing of these cases is most important. It is considered essential that the patient be admitted to hospital for at least the second half of the course of treatment. Complete regression, both of primary and cervical glands, could often be achieved by this method, but if further treatment seemed to be indicated, the dose to the nasopharynx or the neck could be increased by treatment with the small fields to be described later.

In the second group of cases, those with more highly differentiated growths, the lower radio-sensitivity had to be weighed against the prevalence, even in this group, of cervical metastases.

When no glands were palpable in the neck, intensive treatment was given to the tumour by small beam-directed fields planned to irradiate the nasopharynx and local extension of the tumour. Usually 4 portals of entry were used. 2 antero-lateral fields, 6 × 4 cm., angled in 30 degrees and slightly upwards, and 2 lateral fields, 6 × 8 cm., reaching back as far as the external auditory meatus.

A typical arrangement and depth dose distribution is shown in Fig. 13. The tumour dose given in these cases was 5,500 r to 6,000 r in six to seven weeks.

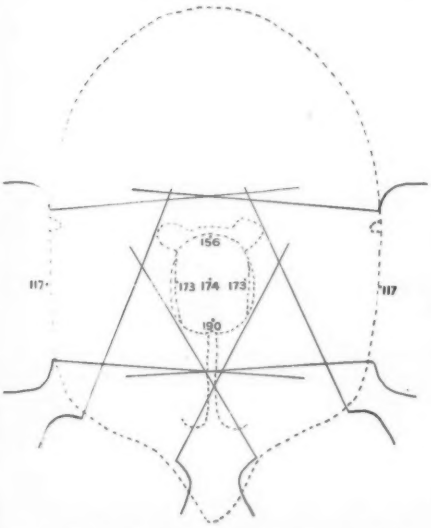


FIG. 13.—Treatment plan and dose distribution for small field irradiation of nasopharynx. Transverse outline 1 cm. below E. A. M.

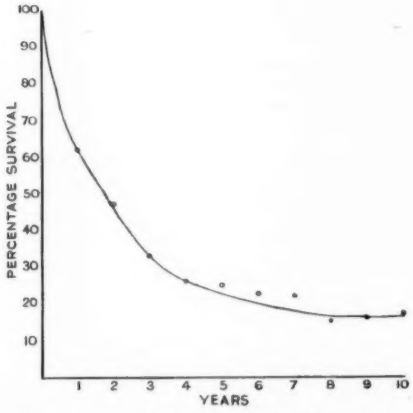


FIG. 14.—Survival curve, showing crude survivals over ten years.

Where glands were palpable in this second group, a compromise was struck. Regional irradiation with the large fields was given up to a depth dose of 2,000 r in two to three weeks, and treatment then continued with small fields both to primary tumour and the palpable cervical glands. Again a tumour dose of 5,500 r in six to seven weeks could usually be achieved without undue general or local reaction.

The factors employed were, 200–250 kV., 10 ma., Thoreus filter or filtration of 1 mm. Cu + 1 mm. Al with a half-value layer of 2·4 or 1·4 mm. of Cu respectively. F.S.D. was 40 cm. with small fields, and 60 cm. with 20 cm. circles.

An extensive primary lesion was not considered contra-indicative to radical therapy, but in 3 cases where distal metastases were present, palliative treatment was given for the relief of pain.

RESULTS

The results of treatment by radiotherapy published in recent reports show that the prognosis is not as hopeless as it was thought to be. New and Stevenson (1943) show 13% five-year survivals, Nielsen (1945) 24%, and Martin and Blady (1940) 25%.

In this series 31 cases were given radical treatment five or more years ago. Of these, 8 cases (25·8%) survived without evidence of cancer for five or more years. Survival periods have been reckoned from the end of the first course of treatment.

Fig. 14 shows graphically the percentage surviving out of the possible total over a period of ten years. The curve has a very steep slope, i.e. a high percentage of deaths during the first two years, and then the curve flattens out. After four years it becomes almost horizontal, indicating that few cases died of cancer after this time.

Classified according to histology, the lympho-epithelioma and undifferentiated carcinoma showed the best five-year results—2 out of 5 (40%) and 4 out of 11 (36%) respectively.

The differentiated squamous-cell carcinomata did badly; only 1 case out of 4 surviving for three years, and none for five. But the transitional-cell carcinomata show by far the worst results. Of the 9 cases, 2 were treated within the last year and both have recurred already, while the other 7 have all died of cancer within two years. Of the 3 reticulum-cell sarcomata, 2 died within the first year, while the third is alive and well five and a half years later. The only plasmocytoma in our series has survived, apparently free from growth, for seven years.

The survival rate is slightly higher (33% against 25%) in those cases where no involved cervical glands were palpable. But the difference is not nearly as great as might have been expected, because of two features. In the first place, cervical glands and in particular the retropharyngeal glands may be involved without being clinically noticeable, and secondly, gland-free cases tend to occur mostly among the less curable types of nasopharyngeal cancer, particularly the transitional-cell carcinoma.

Invasion of the base of the skull carried a bad prognosis. Of 13 cases, 10 have died of the disease, while 3 cases have survived, for five, three and two years respectively.

The question of local recurrence is noteworthy. Late recurrences were not encountered in this series. Of 21 cases which recurred in the treated area, 18 recurred within the first year, and the remaining 3 cases within the second. Of these 21 cases, only one has survived growth-free for five years.

37 cases have died of cancer of the nasopharynx—this figure includes 11 of 20 cases treated within the last five years. 28 cases died with local disease, and in 9 cases (16·6% of the total) distal metastases were present. 21 cases died in the first year, 9 cases died in the second year, and 4 cases in the third year. Thus 34 out of 37 cases in whom the disease was not eradicated died of it within three years.

Conclusions

While the series here reviewed is too small to allow very definite conclusions to be drawn, certain points have emerged.

(1) A five-year cure rate of 25% has been obtained.

(2) The histology of these tumours bears an important relation both to treatment policy and to prognosis. The transitional-cell carcinomata, which appear to be a definite entity, carry the worst prognosis.

(3) Radiotherapy must aim at eradicating the disease with the first course of treatment, as recurrent cases can hardly ever be cured.

(4) The majority of cases dying of cancer have either recurred or died within two years of the first treatment, so that any case surviving for three years after treatment without any signs of disease stands a good chance of permanent cure.

Acknowledgments

I wish to express my sincere thanks to Professor B. W. Windeyer, under whose care these cases were treated, for permission to use the material, and for his help and advice with this paper; and to Dr. A. C. Thackray for his help with the pathological aspects and the photomicrographs.

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Hormone Therapy in Relation to Radiotherapy in the Treatment of Advanced Carcinoma of the Breast

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The great difficulty in modifying the hormonal control of the breast is the complexity of its hormonal relationships. The organ is known to be influenced not only by secretions from the pituitary, ovary and adrenal glands in the normal female, but possibly also by the thyroid and thymus glands. As a result of this multiple control, upset of the balance by removal of one hormone, leads to overaction of another. Thus, deficiency of the ovarian hormone due either to the menopause or castration, may lead to oversecretion of the pituitary or adrenal hormones. Conversely, if there exists an excess of the ovarian hormone, either by natural secretion or therapeutic administration, other parts of the endocrine system may degenerate as a result. Thus any imbalance of hormones achieved by therapy will yield purely temporary results and this is, as we know, usually the case with carcinoma of the prostate.

In the normal adult, the gonadotrophic hormone secreted by the anterior pituitary is generally thought to control the secretion of œstrogens by the ovary and of androgens by the testis. The œstrogens themselves control the development of the secondary sex organs, including the breast and the genitals. An important experimental observation, however, is that an increase in the œstrogen level of the blood either as a result of overaction of the gonad or by therapeutic administration of œstrogens, can inhibit production of further gonadotrophin by the pituitary. The gonadal hormone and the pituitary hormone are thus antagonists. This point and the temporary nature of hormonal imbalance are the important factors when considering hormone therapy. *By the use of œstrogens and androgens the pituitary function can be depressed, but changes are usually temporary.*

In the cyclical female, testosterone has a virilizing effect, and inhibits ovulation and menstruation. This effect is presumably achieved by suppression of the pituitary gonadotrophic hormone (Geist *et al.*, 1941), as seen in the case of the œstrogens. In addition, however, there may possibly be a direct action by the testosterone on the ovary or even neutralization of circulating œstrogens. At the menopause, it often leads to amelioration of the menopausal symptoms, again probably by antagonizing the pituitary oversecretion (Abel, 1945). The complexity of the problems is further increased when it is realized that all normal young adult females excrete androgens in the urine (the quantity being about 50% of that excreted by males) secreted by the adrenal glands. There is possibly a balance between the secretion of androgens and œstrogens in the normal female, and disturbance of such a balance may possibly predispose to the development of breast malignancy.

According to Leucutia (1944) from an analysis of 1,200 cases, the poorest prognosis in breast carcinoma is found in cases occurring between 50 and 59. If we assume that the average age at the menopause is 46½ (Adair, 1947), the poorest prognosis occurs from 3 to 13 years after the menopause. It has also been shown that at the cessation of the menses, it takes up to three years for the œstrogenic hormones to disappear from the blood and urine in the majority of women (Walker, 1944). It is thus suggested that disappearance of the œstrogenic hormones after the menopause exerts an adverse effect on carcinoma of the breast, and this is probably associated with an oversecretion of the pituitary gonadotrophin. Both œstrogens and androgens have been proved of value in postmenopausal cases of breast carcinoma, possibly by suppression of the pituitary oversecretion.

Overactivity of pituitary secretion cannot, however, be so easily incriminated as a growth stimulant in premenopausal cases of carcinoma of the breast. In these cases the normal ovarian secretion is assumed to be present and, in fact, some authorities suggest overactivity of the ovarian hormone as an accelerator of the neoplastic process before the menopause. If this is so, castration might be expected to depress the production of œstrogens and lead to clinical improvement, and the administration of œstrogens might be expected to lead to further activation of the neoplasm. Both these surmises are found to be correct in a proportion of cases. In the absence of exact knowledge, the safest method of treatment in young women is the administration of testosterone. In antagonizes not only the œstrogens but also the pituitary gonadotrophins and is thus the method which is preferred in young women with carcinoma of the breast.

A.—The Results of Œstrogen Administration

This group of cases numbers 152 and represents those patients with advanced cancer of the breast treated by œstrogens between 1945 and 1949 at the London Hospital under the direction of Dr. Frank Ellis.

The average age-group of the patients chosen for œstrogen treatment was high, being over 60. The choice followed a symposium on this subject held by the Royal Society of Medicine in 1944 (*Proc. R. Soc. Med.*, 37, 731), when it was reported that whereas 40% of patients over 60 benefited by the use of œstrogens, only 14% of patients under 60 benefited.

When the age at the menopause of the group is plotted, the average is found to be high. Whereas for the general population this average is from 46 to 47, our observation has been confirmed by many observers that in cases of breast cancer the menopause is most commonly delayed to 50 to 54. This is an important factor in choosing cases for œstrogen therapy, because it has been conclusively shown that administration of œstrogens to cyclical females often leads to activation of the neoplasm. Furthermore, in view of the persistence of œstrogen secretion in the majority of women for at least three years after the menopause, it is considered inadvisable to prescribe œstrogens within five years of the menopause, that is, on the average, before 60.

When the parity of the group is considered it is seen that about a third of all cases occur in nulliparæ. The high incidence of carcinoma of the breast in nulliparæ is well established. Such women are probably not exposed to the fluctuations in hormonal concentrations to which the parous are liable, and such hormonal imbalance may be of protective value as seen later in the results of hormone therapy. The adverse effect of pregnancy on carcinoma of the breast probably depends more on the local effect of lactation than on the œstrogen fluctuation.

In an attempt to assess the value of œstrogen therapy alone as compared with radiotherapy alone, all cases in the series where both treatments were combined have been excluded from analysis of results. In the second place, regression of soft tissue lesions has been taken as the criterion of effectiveness for the purpose of the following analysis.

The 86 cases of soft tissue lesions in advanced carcinoma of the breast treated by stilbœstrol alone have been analysed according to whether the lesions regressed, remained static or progressed. Regression of growth was indicated by healing of ulceration, or decrease in the size of primary growth, skin nodules or secondary glands. Regression of nodules involves bluish discoloration of active pink nodules followed by ultimate shrinkage and disappearance. When the group is considered as a whole, it is found that 55% of cases showed regression of lesions, whereas 29% showed progression of lesions and 16% remained static.

When separated into the over-60 group and under-60 group, regression is found to occur in 59% of the older group but only 44% of the younger group. These figures are considerably higher than the 40% and 14% respectively quoted at the R.S.M. symposium in 1944, but it must be remembered that their series included cases of distant metastasis also. It is also seen that with a longer postmenopausal interval, there is a higher proportion of cases showing regression. The high proportion of cases showing progression of the disease among the younger age-group suggests that *it is dangerous to use œstrogens in the treatment of menopausal symptoms in patients with quiescent carcinoma of the breast.*

No significant difference is obvious between the early menopause and the late menopause cases or between nulliparæ and multiparæ. It is seen that with a longer history (and thus presumably a more slowly growing neoplasm) the proportion of cases regressing is considerably higher. This is possibly a factor in the better response to œstrogens in older women where the slowly growing scirrhous type of neoplasm is more commonly seen. This observation is contrary to that of Haddow and his colleagues (1944), who consider the best response to be in the case of highly cellular neoplasms.

When we consider the results according to dosage, the group is divided into those cases receiving 1 to 2 mg. daily and those receiving 20 mg. daily. The results for these widely differing dosages are almost identical suggesting that the lower dose is sufficient to exert the maximal effect in counteracting the pituitary secretion.

Incidence of complications in œstrogen therapy.—The common ones are nausea or vomiting, uterine bleeding and pigmentation of the nipples. Nausea or vomiting are noted in 16% of all cases, size of the dose making no difference. This is less than the figure of 25% quoted by Adair (1949). The incidence of uterine bleeding appears fairly similar with either dosage and is noted in 35% of the total. The figure is lower than the 50% quoted by Herrmann and his colleagues (1947*b*). Bleeding after the menopause with œstrogen therapy is said to occur essentially as a result of œstrogen withdrawal, i.e. on

stopping its administration. In this series, many of the cases developed the symptoms while taking the drug regularly. That larger doses of the hormone induced no more bleeding than the smaller doses suggests that the smaller dosage is sufficient to induce any endocrine changes that may be expected from œstrogens. In some cases, however, nausea, vomiting or uterine bleeding were so excessive that the patient refused to carry on with the therapy. The symptoms were often severe at the beginning of treatment and diminished later if the patient persisted with the drug. Replacement of high by low dosage had little effect in checking them. Pigmentation of the nipples was seen in the majority of patients. The colour varied from light brown to black with scabbing of the surface of the nipple. In a small proportion, in addition, pigmentation of old scars or of the striæ gravidarum was seen.

Generally speaking, it was noted that the primary growth responded most markedly, secondary skin nodules a little less so and glandular metastases least of all. Sometimes nodules regressed in one part and spread in another. Nodules of longer standing usually regressed before the more recent ones. In the cases of soft tissue regression, commonly the neoplasm became active again after a period of one to two years, and distant metastases developed in spite of the œstrogen administration. In the case of bone metastases developing during œstrogen administration, there appeared to be no sign of relief of pain or recalcification of such metastases by continuing the drug. Deep X-ray therapy, therefore, was used for relief of pain in these cases at the London Hospital. There is no doubt, however, as to the value of œstrogens in a high proportion of soft tissue growths in older women. In 13 cases of bone metastases given stilbœstrol, death occurred on the average five months after administration was begun, only 4 cases surviving over twelve months.

The most interesting observation concerns the treatment of pulmonary metastases. Out of 25 recorded cases of pleural or lung metastases treated by œstrogens, there were 9 who survived over twelve months. In most of these cases, lung metastases and effusions are seen to regress. In addition to these 9 cases, there are also a further 3 cases who are still alive six months or more after the development of pleural effusions and who show decrease in the size of the effusion. A total of 12 cases out of 25 with lung or pleural metastasis thus show benefit. These results are remarkable in view of the fact that the general expectation of life after developing pleural or pulmonary secondaries to carcinoma of the breast is only three months on the average. There are, however, 14 cases in the series where the patient is certified as dying of lung or pleural metastases, where stilbœstrol had been administered for three or more months for other metastases. A prophylactic effect against pulmonary metastases is therefore not proved.

B.—The Results of Androgen Administration

56 cases of advanced cancer of the breast were treated by testosterone, the male hormone. The average age-group of the patients chosen for this form of treatment was lower than for the œstrogens, the younger age-group cases being generally considered more suitable for androgen therapy. When we consider the cases in relation to their menstrual state, the distribution shows about half the cases to be cyclical.

The choice of a criterion of effectiveness for the hormone was difficult. Whereas the original successfully treated cases reported by Ulrich in 1939 and Loeser in 1940 were of soft tissue metastases, the later work of Herrmann, Adair and Woodard (1947*a*) in the U.S.A. suggested that the indication for the hormone was essentially the relief of pain from bone metastases. It appears, however, that in the doses recommended by Adair and his colleagues, that is, 1,200 mg. monthly, the cost of treatment, viz. £45 for a three-month course, does not justify its use for bone metastases. These can be treated just as effectively by a two weeks' course of radiotherapy, with less expense and unpleasant side-effects. Therefore, in this series, testosterone has not been used for the treatment of bone metastases. Nevertheless, Adair (1947), reporting on 200 cases treated by large doses of testosterone, claims that relief of pain from bone metastases occurs within two weeks in the majority of cases. It is followed by recalcifications in many and Adair believes that life may be prolonged two or more years in cases of widespread metastases. On the other hand, he states that although soft tissue metastases may occasionally disappear in a striking fashion, the results generally are poor.

In spite of this conclusion, in our series testosterone was used, either with or without radiotherapy, in an attempt to control the growth of soft tissue metastases from carcinoma of the breast. For the purpose of the analysis, in cases where regression was noted for a few months followed by progression of the disease, the case is noted as a progression. Altogether, there were 26 cases in which the reaction of metastatic nodules could be assessed. In the case of primary breast growth and metastatic glands, these were treated by irradiation, testosterone being tried for rapidly growing metastatic nodules not easily controlled by

irradiation. Of the 26 cases, 39% showed regression and 46% showed progression, 15% remaining static.

Regression of nodules following testosterone is unlike that which follows deep X-rays. In the latter, the nodule is involved in the erythematous reaction and after desquamation it appears paler and flatter. In the case of testosterone, total disppearance of the nodule is noted only with smaller lesions. In the case of larger nodules, the centre of the nodule falls in, to which I have given the description of "umbilication" and the nodule assumes a bluish colour. Later it shrinks flat with the surface of the skin, but the nodule remains covered with a blackish greasy scab. This inactive appearance is totally different from the pinkish, convex active nodule. In the case of multiple nodules responding to testosterone, they often scab, but in more advanced cases ulceration of the old nodules occurs, although no new nodules appear. Regression of nodules is slower than with œstrogens and usually the older nodules disappear first. Nodules may regress for a few months and then reappear.

With regard to the development of metastases during testosterone administration, the results are as poor as in the case of the œstrogens and possibly worse in one aspect. Out of 24 cases where there were *no signs of distant metastases* when the patient was put on to testosterone, 8 cases (i.e. 33%) died of cachexia or distant metastases after intervals varying from one to eight months. A further 6 cases developed pleural effusions but are still alive, in 2 cases with regression of the pleural effusion. These latter 2 cases show survivals of 22 and 28 months respectively since administration of testosterone. Thus, although in this group 6 cases showed regression of nodules, the development of distant metastases was not prevented, and, in fact, the development of pleural effusions may have been accelerated. This fact will be referred to later. X-ray castration was used as an adjunct to testosterone in most cases that were still cyclical. Castration is of assistance in controlling the growth since it decreases the production of œstrogens in cyclical cases, although the adrenal cortex may take up œstrogen production when the ovary fails (Snapper, 1947).

There are three possible modes of action of testosterone: (*a*) Inhibition of the gonadotrophic pituitary hormone; (*b*) Depression of œstrogen production or neutralization of circulating œstrogens; (*c*) Creation of a hormonal imbalance. It is possible that each method may be involved at a different age-period. Farrow and Woodard (1942) favour the theory that testosterone acts by creating a hormonal imbalance. They showed that when the ages of incidence of bone metastases in carcinoma of the breast are graphed, there are least cases from 40–55, the years of the natural menopause. They assume that this is due to the phase of hormonal imbalance which begins several years before and ends several years after the natural menopause. Testosterone may act similarly, and if, at first, metastases respond but later become reactivated, it has been observed that switching the patient to œstrogens may again control the growth, by swinging the hormonal balance (Adair, 1949).

An essential concomitant of testosterone therapy is the development of virilization or masculinization. The signs consist essentially of amenorrhœa, hoarseness, acneform eruptions and hirsuties. Amenorrhœa develops more rapidly in patients nearer the menopause. Hoarseness is at first periodical but later continuous. The acneform eruption affects principally the face and shoulders and is associated with a seborrhœic tendency of the skin. Hirsuties affects principally the beard area and the legs. All these changes are temporary and recede within a few months of discontinuing the drug. The dosage necessary for these changes varies according to the individual, but my own experience is that the changes are more marked in the dark-skinned than in the fair-skinned. In the most successful cases of the series, they developed on a dosage of 100 mg. monthly by implantation, but in the majority they do not appear until doses of 300 mg. or more are given monthly for a period of over two months. Generally speaking, successful virilization was associated with tumour regression but this is not always so. An important observation is that in 2 cases hirsuties developed around the region of the testosterone implant. This suggests a local effect of the hormone. In addition to these unpleasant side-effects of testosterone, there are beneficial effects. The patient notes an increase in energy, a feeling of well-being and an increase in libido. There is also a tendency to gain in weight and to puffiness of the face. The weight that is gained is lost after stopping the drug and is thought to be associated with retention of water, nitrogen and electrolytes, possibly due to upset of the adrenal function (Geist *et al.*, 1941). In this connexion, the development of pleural effusion in a high proportion of treated cases may be mentioned again. It develops usually with the introduction of high dosage, viz. 800 mg. monthly in our cases. In 2 cases, the effusion regressed later and thus may be in some cases a non-malignant effusion associated with fluid retention.

The dosage used at first in this group of cases was 100–200 mg. testosterone by subcutaneous implantation at monthly intervals. The pellet takes about six months to absorb but the most rapid absorption occurs soon after the implantation when the surface area of the pellet is greatest. It has been the practice, therefore, to crush the tablet after insertion

so that absorption occurs uniformly over a month or two. In cases where such doses are unsuccessful, 100 mg. testosterone propionate has been injected twice weekly which yields 800 mg. monthly. Many of the series in the literature report successful results with doses of around 500 mg. monthly. On the other hand, Adair recommends doses of 1,200 mg. monthly as being optimal. Oral use of testosterone is wasteful although the drug is absorbed by the mucous membrane when it is sucked and allowed to dissolve in the mouth. The effectiveness is, however, only 50% of the same dose given by injection or implantation.

Some Successful Cases

Case I.—Patient attended, aged 67, with a history of a left mastectomy twenty-three years before. In October 1944 she developed a recurrence in the opposite breast and this was treated by deep X-rays. November 1945 (Fig. 1A) shows multiple metastases in the left lung. Stilbœstrol 5 mg. four times per day was prescribed. Five months later (Fig. 1B) showed disappearance of the metastases. Stilbœstrol was stopped.



Fig. 1A (*Case I*).—22.11.45.

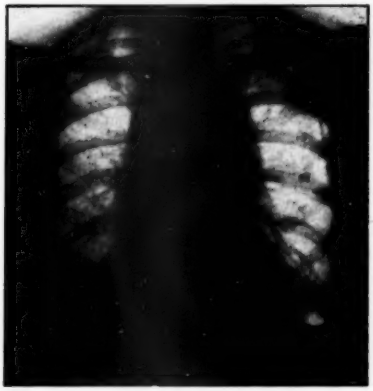


Fig. 1B (*Case I*).—4.4.46.

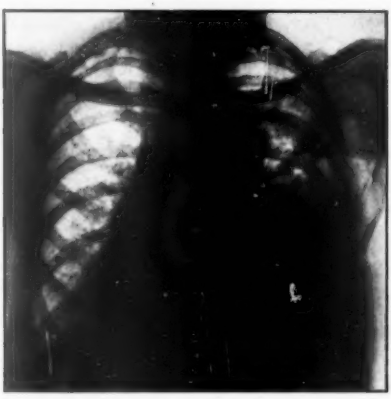


Fig. 1C (*Case I*).—6.6.47.

A further nine months later she showed recurrence of the metastases and a pleural effusion. Stilbœstrol was recommenced.

A further five months (Fig. 1C) later showed increase in the fluid and spread of the lung metastases. The patient finally died in October 1947, *two years* after developing lung metastases.

Case II.—Patient attended in July 1948, aged 66, with a large ulcerated mass in the right breast.

Radiograph chest three months later (Fig. 2A) showed multiple opacities in both lungs and a right pleural effusion. Stilbœstrol 0·5 mg. q.i.d. was prescribed.

Radiograph chest *one year and nine months* later (Fig. 2B) showed partial disappearance of the metastases. The patient was so well that the primary breast growth was recently treated by deep X-rays palliatively and the patient is still well.



FIG. 2A (*Case II*).—1.10.48.

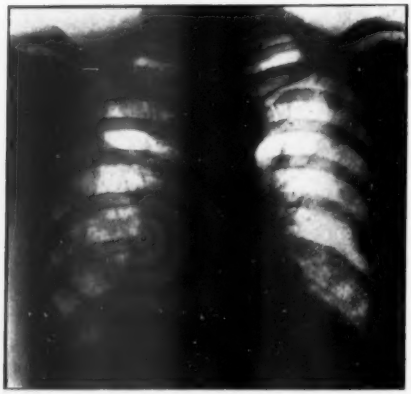


FIG. 2B (*Case II*).—12.7.50.

Case III.—Patient attended July 1945 for post-operative irradiation after right radical mastectomy. She was aged 53 and nine years post-menopausal.

In January 1947 she developed metastases in the supraclavicular fossa which were treated by X-rays.

Radiograph chest, October 1947, showed a shadowing extending out from both hila and discrete masses in the right lung field—diagnosed as lymphangitis carcinomatosa.

Three months later the patient developed pelvic metastases which were treated by X-rays and stilbœstrol 5 mg. q.i.d. was prescribed. Radiograph chest twenty-two months later showed clearing of the lung fields and of the hilar shadows, although the right diaphragm was raised.

The patient finally died in January 1950, *two years and three months* after developing the lung infiltration.

Case IV.—Patient attended January 1946, with a history of a right mastectomy three months previously. She was aged 52.

Radiograph chest showed shadowing at the right lung base. Dienœstrol 0·5 mg. q.i.d. was prescribed. In April 1946 palliative X-rays were given to the primary mass in the breast and in March 1947 to the left supraclavicular glands.

Radiograph chest eighteen months after the first film shows an effusion at the left base and an interlobar effusion. Increased lung markings suggested carcinomatosis. The patient finally died *one year and eight months* after the first development of lung metastases.

Case V.—Patient attended in May 1946 with a mass in the left breast and mutiple skin nodules. She was aged 72.

Repeated X-ray treatments were given to the chest wall and axillary glands.

Radiograph chest March 1948 showed a left pleural effusion. The patient also showed active skin nodules. Stilbœstrol 5 mg. q.i.d. was prescribed.

Radiograph chest *two years later* showed disappearance of the effusion. All the skin nodules have meanwhile regressed. The patient is still alive and well.

Case VI.—Patient attended March 1948 with a mass in the right breast and axilla. She was aged 60.

Radiograph chest March 1948 showed a right-sided pleural effusion. Stilbœstrol 0·5 mg. four times daily was prescribed and although the axillary mass decreased in size, the breast mass remained unchanged.

Radiograph chest fifteen months later showed diminution in the right pleural effusion but, in addition, an effusion at the left base. The patient died *two years after* the original effusion.

Case VII.—Patient attended in February 1948, with a history of left mastectomy six years previously. She was aged 43 and was still cyclical.

Radiograph of chest showed right pleural effusion. Malignant cells were demonstrated in the fluid. Patient had hæmoptyses. She was given 1,200 mg. testosterone propionate monthly.

Radiograph chest five months later showed regression of the effusion. Testosterone was stopped three months later.

Radiograph of chest seven months after stopping testosterone showed recurrence of the pleural effusion.

Testosterone propionate was recommenced at the rate of 800 mg. monthly.

Radiograph chest twenty-two months after the original effusion still showed fluid present.

Patient is still alive *two years and a month* after the original effusion.

Case VIII.—This patient first attended in 1946 when she was aged 36. There was a history of a left radical mastectomy nine months before and when first seen, this patient had nodules around the scar and glandular metastases in the right axilla and left supraclavicular region. She was given X-ray treatment to recurrent groups of nodules between September 1946 and March 1948. Implantations of testosterone 100 mg. monthly were begun in September 1948 when further X-ray treatment was no longer practicable. Within three months, the nodules had become flatter and in the fourth month, the patient showed acne, facial hirsuties and a definite gain in weight although the periods were still regular.

After twelve months of testosterone, the patient developed a pleural effusion at the right base and although the nodules were under control, the opposite breast showed neoplastic infiltration. Large doses of testosterone propionate by injection, 900 mg. monthly, were given and three months later the effusion had almost disappeared. It was decided to treat the right breast by deep X-rays because of the slowness of its response to testosterone.

Case IX.—Patient first attended February 1948, with a history of a left mastectomy eighteen months previously. She was aged 46 and was still cyclical. Secondary deposits in the sacrum were suspected, and treated by irradiation.

Radiograph chest February 1948 (Fig. 3A) showed multiple rounded opacities in both lung fields. Testosterone implantations 100 mg. monthly were begun four months later.

Radiograph chest over *two years later* (Fig. 3B) showed no progression in the metastases. The patient is still alive and very well. She is completely symptom free. It is suggested that menopausal changes and the testosterone held up the spread of lung metastases.

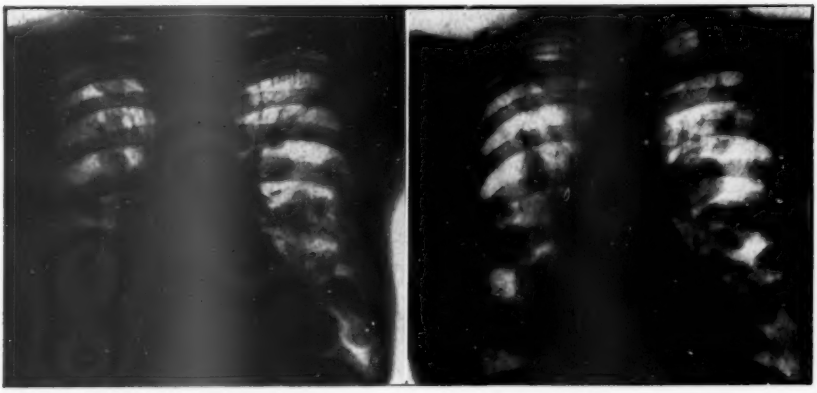


FIG. 3A (*Case IX*).—27.2.48. FIG. 3B (*Case IX*).—31.7.50.

Case X.—Patient attended October 1943, with a mass in the right breast and multiple skin nodules. She was aged 47 and still cyclical.

She was treated by deep X-rays to the right chest wall with temporary regression of the nodules.

Radiograph chest December 1944 showed an opacity in the right lower zone. ? secondary, ? inflammatory.

Radiograph chest twenty-one months later showed increase in the shadowing at the right base and an opacity at the right apex in addition. She was put on to dienœstrol 5 mg. q.i.d.

Radiograph chest a further fifteen months later showed no change in the opacities. Dienœstrol was stopped.

Radiograph chest a further six months later showed multiple opacities in the lung fields, left-sided effusion and radial shadowing suggesting lymphatic spread. Stilbœstrol was recommenced but the patient died *four years after* developing the original lung condition.

It is suggested that menopausal changes and the stilbœstrol held up the spread of lung metastases.

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Section of Comparative Medicine

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DISCUSSION ON CLOSTRIDIAL TOXINS IN RELATION TO TYPE-SPECIFICITY FOR DIFFERENT SPECIES OF HOST

Dr. C. L. Oakley: I have little doubt that the title of this Discussion is misconceived, for I hold that the nature of the toxins produced by the various species of clostridium has little or nothing to do with type-specificity for particular hosts. I might produce the maximum effect by leaving the matter there, but I find it much more interesting to speculate on the factors that do determine host-specificity, for some of these seem to me to depend on the mode of life and characteristics of the host. Taking general considerations first, the species of clostridium, if they are to infect, must be present in the host environment; they must be present, either actually or potentially, in numbers sufficient to lead to infection, and they must encounter in their host conditions in which they can grow.

Cl. welchii type A is ubiquitous: it occurs in soil, in the intestine of man and animals, in manured ground, in dust, and in the muscles of normal dogs. Gas gangrene is not produced by it in animals or man unless the oxidation-reduction potential of the tissues in which it occurs is sufficiently reduced; this is usually produced by an extensive wound of muscle, usually a war wound carrying the organism in and rendering large masses of muscle anoxic. Domestic and laboratory animals suffering such injuries are usually killed before gas gangrene occurs, but cases have been reported in domestic animals, and experimental gas gangrene is readily produced in dogs. The host-specificity of type A is certainly more apparent than real, and depends on the relatively small risk of wounding in animals as compared with man in modern war.

Cl. welchii type B, the cause of lamb dysentery in sheep (a few cases of a similar disease have been reported in foals), has a much more limited distribution than type A. It has been found in the intestinal content and discharges of infected lambs, in the soil of infected farms and on the udders of ewes during outbreaks; it has so far not been recovered from farms on which lamb dysentery occurs outside epidemic periods. The usual view is that ewes readily contaminate themselves with the infecting organism from the ground soiled with the discharges of infected lambs, and that the lamb is infected during suckling from the udder and wool of the ewe, though this may not be the whole story. The disease is limited to lambs in the first few days of life, and very few cases occur after the first week. We have good reason for supposing that very great changes occur in the alimentary canal of the lamb in the first few days of life; protein is readily absorbed from it for a few days, but not afterwards, and it is very tempting to believe that after the first few days proteolytic enzymes appear in the alimentary canal, and destroy the few *Cl. welchii* type B ingested before they can multiply (possibly in the small intestine) to an infecting dose. My veterinary colleagues inform me that a dose of *Cl. welchii* type B that will readily produce a disease closely resembling lamb dysentery when injected intraduodenally in guinea-pigs completely fails to infect guinea-pigs when administered by mouth. The organism then has a very short time in which to infect; any reduction in the probability of an animal picking it up in the vulnerable period will greatly reduce its chance of becoming infected. It is common practice to remove calves from their mothers at birth and bucket-feed them, so that even in infected areas the chance of calves picking up infection from their mothers is small; moreover cows are much more selective feeders than sheep, so that while sheep might feed from the same small area of a field, thus increasing the chance of contamination, cows are likely to move freely over a field and may even miss the infected patch altogether.

Cl. welchii type C, the cause of struck in adult sheep, particularly after lambing, is an organism of very limited distribution, almost confined to the Romney Marsh. Here few animals but sheep are kept, and this may account for the fact that there are no records of *Cl. welchii* type C infection in other species.

Cl. welchii type D is the cause of enterotoxæmia in sheep and goats. It is generally distributed and can readily be recovered from the soil of infected farms, from ewes' udders and the intestines of infected sheep. The disease seems to occur with particular frequency in well-fed sheep, older than those in which lamb dysentery occurs: this suggests that many of the organisms get through the stomach enclosed in food—it has indeed been claimed that lambs can be infected by feeding them with *Cl. welchii* type D plus casein; the casein clot protects the organisms from the gastric acid and enzymes. Again the fact that cows are more selective than sheep and that calves are bucket-fed, may be of importance; but it is more likely that cows' feeding habits render infection less likely. The cow curls its tongue round the plant, and tears the upper parts of it off; sheep and goats feed close to the ground, and far more readily eat infected soil with their food.

I pass over type E, as not certainly pathogenic. *Cl. welchii* type F, the cause of enteritis necroticans in man, is markedly heat-resistant, its spores withstanding boiling for from one to four hours. In Germany of recent years numerous cases of a disease in man resembling lamb dysentery have been described as occurring after the ingestion of large meals containing tinned rabbit, tinned fish and fish paste. It seems clear that what occurs is that the food contaminated with *Cl. welchii* type F is heated to boiling for two hours: all the aerobes are killed off, and the *Cl. welchii* type F multiply exceedingly in the anaerobic conditions in the slowly cooling liquor. When they are eaten enclosed in large masses of food, they are protected from the gastric acid and enzymes and produce the infection.

Finally we might consider *Cl. tetani* and *Cl. œdematiens*. Though, as far as I know, *Cl. tetani* shows no distinct host-specificity, tetanus is much commoner and more fatal in horses that it is in cows; like others, we have found that "normal" tetanus antitoxin is rare in horses, but common in cows; may not ruminant digestion in cows allow *Cl. tetani* to grow and immunize the cow, while in horses the organism is rapidly destroyed in the single stomach?

Cl. œdematiens type A exhibits no remarkable type-specificity; it produces gas gangrene in man, sheep and asses at least. *Cl. œdematiens* type B is a normal inhabitant of the livers of sheep and cows in areas where black disease is prevalent, but is unable to produce black disease (infectious necrotic hepatitis) in sheep unless the liver is attacked by the liver fluke *Fasciola hepatica*. Here the infectivity of the bacterium depends on the provision of proper conditions for its growth, and therefore indirectly on the host-specificity of *Fasciola hepatica*.

I think it clear enough that though clostridial toxins play an exceedingly important part in deciding the form of infection produced by a particular type of a species of clostridium, they have little importance in determining whether an infection is set up or not.

Miss Helen E. Ross (*The Wellcome Physiological Research Laboratories, Beckenham*): At least twenty clostridial toxins have now been identified, and fourteen are known to have lethal significance in toxæmias of man and animal species. The previous speaker emphasized that no single toxin can be regarded as host-specific, but four are exceptional, in that they are the principal agents in fatal toxæmias of sheep: braxy, necrotic hepatitis and enterotoxæmia.

Two of the toxins, *Cl. septicum* lethal toxin and *Cl. œdematiens* α toxin, are known to be related also to clostridial myositis in many host species, but two have been demonstrable only in relation to enterotoxæmia: the latter are the β toxin and ϵ toxin of *Cl. welchii* which, as shown in Table I, are formed by the sub-species or types B, C, D and F.

TABLE I.—*Cl. welchii* β AND ϵ TOXINS IN RELATION TO TOXÆMIAS IN HOST SPECIES

Sub-species type	Toxin	Toxæmia	Host species
B	β	Lamb dysentery	Sheep (lambs)
C	,,	Struck (enterotoxæmia)	,, (adult)
F	,,	Enteritis necroticans	Man
B	ϵ	Lamb dysentery	Sheep (lambs)
D	,,	Pulpy kidney disease	,, (weaned lambs)
D	,,	Enterotoxæmia	,, (adult)
D	,,	Enterotoxæmia	Goats

Neither toxin alone is host-specific, but when formed together by *Cl. welchii* type B, they

have up to the present time been demonstrable, almost exclusively, in only one host, the very young lamb affected with lamb dysentery.

This combination of toxins has certain peculiar characteristics, and a short description of these seems appropriate to this discussion.

Characteristics of toxins.—Both β toxin and ε toxin have lethal and necrotizing properties, and are demonstrable only by the use of *in vivo* test methods, involving for example, the intravenous injection of mice and the intracutaneous injection of guinea-pigs and rabbits. Both are neutralized only by their specific antitoxins.

Toxin formation in vitro.—β toxin is formed and becomes demonstrable in filtrates of cultures on meat broth medium during the active growth phase of the organism, but may be no longer demonstrable if incubation, at 37° C., is continued beyond twenty-four hours. Conversely, ε toxin may be demonstrable only after the active growth phase has passed; this, however, is due to the fact that it is formed comparatively slowly from a non-toxic precursor, ε prototoxin (Turner and Rodwell, 1943), formed in the earliest phases of growth of the organism.

This transformation of prototoxin into toxin can be brought about by incubating the culture fluid containing the former, in contact with trypsin (5% v/v) at 37° C. for half an hour. This treatment destroys β toxin so that, although this toxin was demonstrable in the fluid beforehand, it can no longer be detected in the treated fluid, and ε toxin alone is demonstrable.

Selective media.—A similar reversal of the toxin content of culture fluids can be obtained by the use of selective media; one designed to be the optimum for β toxin, and the other for ε toxin. For example, a 1% (w/v) glucose broth medium favours the formation of β toxin but is inhibitory for ε toxin: and, conversely, a meat broth medium, to which 5% (v/v) trypsin has been added at the time of inoculation, is the optimum for ε toxin and inhibitory for β toxin. A medium prepared from a tryptic digest of casein with hydrolysed starch added has also been found to be selective for the formation of ε toxin but completely inhibitory for that of β toxin.

Toxin formation in vivo.—The relationship between the nature of the medium and the type of toxin formed *in vitro* is apparent also *in vivo*, in lambs affected with lamb dysentery. Thus, in the intestinal tract of lambs infected with *Cl. welchii* type B, the type of toxin formed depends upon the age of the lamb, upon the food ingested, whether colostrum, milk, or a mixture of grass and milk, and upon the relative stage of development of its digestive enzyme system.

β toxin alone has frequently been demonstrable post mortem in the bowel contents of lambs dying within a few hours or a few days of birth; and ε toxin alone in those of lambs dying when 10 to 14 days old.

It has not been possible to isolate *Cl. welchii* type B from older lambs and it is evident that organisms of this type persist in the lamb only while it is milk-fed. It has been found, moreover, that strains of this type can be isolated more frequently from the lower levels of the lamb's intestinal tract than from the higher levels. A series of cultures was made from the stomach, duodenum and ileum of twenty-three lambs less than 2 weeks old, and an average of three single-colony cultures was isolated from each of these sites. The distribution of the strains according to their type is shown in Table II.

TABLE II.—DISTRIBUTION OF *Cl. welchii* SUB-SPECIES IN THE INTESTINAL TRACT OF LAMBS

Site	No. of strains examined	No. of strains identified			
		Type B	D	A	Non-toxic
Stomach and duodenum	125	24	78	17	6
Ileum	120	98	15	6	1

A statistical examination of the figures undertaken by Dr. C. L. Oakley shows where Yates correction for continuity is applied, $\chi^2 = 92{\cdot}6$; $n = 1$; $P < 0{\cdot}001$. The numbers of type B and type D strains recovered from the different sites were therefore significantly different. The obvious predilection of type B strains for the lower levels of the intestinal tract, while suggesting that this type originates there as a variant of a more stable type, shows clearly that it is only the parent clostridial species or sub-species and not their individual toxins which can have any degree of specificity for any one host species.

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In both human beings and sheep, infections with *Cl. welchii* usually assume one or other of two major forms: a rapidly spreading myositis following deep trauma, or a severe, sometimes necrotizing, enteritis. The former of these is more often seen in man, the latter in lambs and young sheep. Immunological studies on the strains of bacteria recovered have shown that these distinctive clinical manifestations are associated with infections with different variant forms or "Types" (Wilsdon, 1931) of this clostridium, and the toxigenic analysis of their manifold bacterial products has led to the belief that the characteristic muscle, kidney and intestinal lesions are the results of the actions of specific toxins. Infections with *Cl. welchii* thus present two large general problems towards whose solution considerable progress has already been made. For the investigator of epidemics or epizootics, the main concern is as usual with the natural reservoirs of infection, the modes of transmission and the portals of entry of the various types of the organism. For the pathologist, the chief interest hinges on the possibility raised by antigenic analysis of being able to attribute specific organ lesions to the operation of distinctive toxins.

Of the several antigenic substances present in toxic filtrates of *Cl. welchii* type A, it now seems likely that the α-toxin contributes predominantly to its lethal action. Much work substantiating this conclusion was carried out during the war by Hartley and Evans at Hampstead. In the main, their evidence was derived from experiments of two different, but complementary, kinds. In the first, the virulence for guinea-pigs, on intramuscular injection, of each of a series of thirty strains of this organism was compared with its capacity to produce α-toxin, θ-hæmolysin and hyaluronidase on culture (Evans, 1945). The thirty strains showed wide variations in their ability to form these substances; some strains failed to produce any θ-hæmolysin or hyaluronidase. When virulence for the animals was correlated with these variables, however, its closest association was with α-toxin production. The second experiments concerned the measure of protection afforded to infected guinea-pigs by antisera that contained predominantly or exclusively the α-antitoxin, the θ-antihæmolysin and anti-hyaluronidase respectively (Evans, 1943*a* and *b*). These left no doubt that in this experimental infective myositis the only effective protective agent was the α-antitoxin.

Roughly contemporary with Hartley and Evans' immunological work was the important discovery by Macfarlane and Knight (1941) that the α-toxin of type A organisms is a powerful lecithinase capable of breaking down lecithin into a diglyceride and phosphorylcholine. Less effectively, this enzyme also hydrolyses the related phosphatide sphyngomyelin—a substance which resembles lecithin in containing phosphorylcholine (Macfarlane, 1942). It is generally agreed, however, that the α-toxin has no significant action on phospholipids of the cephalin group which do not contain phosphorylcholine (Macfarlane, 1942; Zamecnik, Brewster and Lipmann, 1947). It seems clear, therefore, that the important point has been established that a powerful toxin is also a narrowly specific enzyme capable of hydrolysing substances which are known to be essential constituents of all cell membranes.

There is further evidence that supports the belief that the α-toxin acts as a lecithinase *in vivo* as well as *in vitro*. If the toxin is mixed with an emulsion of lecithin before injection into the skin, it loses much or all of its toxicity—the enzyme presumably undergoing prior fixation to an excess of its substrate (Wright and Hopkins, 1946). Injection of lecithin emulsions into the blood stream of mice and dogs at about the same time as α-toxin likewise has a beneficial effect on the toxæmia—probably because of the same substrate-fixation mechanism (Zamecnik *et al.*, 1945). More direct evidence has been obtained from isolated heart perfusion experiments, however, for the addition of α-toxin to the circulating saline both killed the heart and led to the liberation of phosphorylcholine into the perfusate (Wiatt and Wright, 1947). It seems evident, therefore, that the α-toxin of *Cl. welchii* is not only the most important constituent of toxic filtrates from type A cultures, but also that it acts as a lecithinase *in vivo* as well as *in vitro*. Probably the other lecithinase-producing clostridia, *Cl. œdematiens*, *Cl. sporogenes* and others, cause tissue damage in the same way (Miles and Miles, 1947; Oakley *et al.*, 1947).

The changes undergone by tissues, and particularly by muscles, exposed to type A toxins has been studied on several occasions (Govan, 1946; Kettle, 1919; Robb-Smith, 1945). During the past war, Robb-Smith made histological examinations of muscles obtained from both gas-gangrene patients and rabbits intoxicated experimentally. The fibres in such muscles show fragmentation and disruption of their sarcolemma, together with karyolysis of their nuclei. These changes, evident within a few hours of the inception of intoxication, were soon followed by others that involved the reticulin and collagen fibrils which form a conspicuous feature of skeletal muscle. After twenty-four hours, many of these fibrils had disappeared; only the elastica remained. In experiments in which thinly-cut frozen sections of muscle were exposed to this toxic filtrate, it was found possible to separate the destructive properties of two constituent enzymes by selective inhibition of the lecithinase by removal of the ionized calcium essential for its activity. When toxic filtrate was added to citrate buffer, in which

the α-toxin was rendered inactive, the reticulin and collagen were digested as rapidly as in the uncitrated buffer, but the other signs of cell damage were less pronounced. These findings suggested that the collagenase and lecithinase activities of such filtrates are quite distinct, and this conclusion has since been confirmed by the immunological identification of the κ-toxin (Oakley *et al.*, 1946). How far this κ-toxin contributes to the intoxication in clostridial myositis due to type A strains is still not wholly settled (Oakley *et al.*, 1948). It unquestionably adds to the destructive properties of such toxic filtrates but studies with dissociated α- and κ-antitoxins have shown that it possesses little or no lethal power, because an antiserum that contains α-antitoxin but no anti-collagenase is highly effective in protecting infected guinea-pigs, whereas an antiserum that contains anti-collagenase but no α-antitoxin was unable to do so (Evans, 1947). While the collagenase κ-toxin accelerates the disruption of infected muscle, its position so far as tissue intoxication is concerned seems more nearly akin to that of hyaluronidase than to that of the α-toxin; both the former destroy intercellular constituents while the latter attacks an essential component of the cells themselves.

The second great group of *Cl. welchii* diseases, "lamb dysentery", "struck", "infectious enterotoxæmia of sheep", together with the acute necrotizing enteritis of human beings recently described by Zeissler and his colleagues in Germany (1949), presents clinical and pathological features that are wholly different from the typical clostridial myositis of "gas gangrene" of man and the related "blackleg" of cattle and sheep. From the epizootic standpoint, three characteristics of this group of enteric intoxications seem to be of primary significance. Firstly, they depend on enteric infections with less widely occurring types of *Cl. welchii*. Taylor and Gordon (1940) examined more than 1,000 cultures of this organism that had been recovered from the intestinal contents of normal human beings, cattle, sheep and other domestic animals and found only 3 strains of type B and 10 of type D; the vast majority were of type A. It would thus seem that, so far as their distribution is concerned, a rough parallel might be drawn between the *Cl. welchii* variant types and the coli-typhoid group of organisms—types B, C and D being related to type A much in the same way that typhoid and paratyphoid bacilli are to the colon bacillus. Secondly, in these clostridial infections of the gut, bacterial invasion of the local tissues is relatively inconspicuous except as a terminal event. Thirdly, the responsible bacteria seem to bring about injuries by liberating potent enterotoxins while they are multiplying in the digesting intestinal contents. I shall now consider these points in turn.

The intestinal lesions in "lamb dysentery" have been studied by many, and I need here only refer to them briefly. Gaiger and Dalling (1921) and Pool (1929) have described them as ranging from a mild congestion of the inner lining to a necrotizing enteritis in which large areas of mucous membrane of both small and large intestines have been sloughed away. From the ulcers so formed Dalling was able to recover almost pure cultures of *Cl. welchii* type B. But in spite of the wide loss of epithelium, the degree of tissue invasion by the clostridia was small—what there was seemed to have been a terminal event. Hare and Glynn (1927) described the early stages of the lesion as petechial hæmorrhages, usually near the distal ends of the villi, followed by necrosis of the overlying epithelium. They, too, emphasized that clostridia were not present in the submucosal tissues during the initial stages of the lesion.

The morbid morphological changes found in animals dying from the enteritis due to *Cl. welchii* type C have been described by McEwen and Roberts (1934*a*). In this disease, generally known as "struck", the principal lesion is a progressive enteritis, culminating in some animals in ulceration extending over many feet of gut. The lesion begins as a necrosis of the superficial epithelium and progresses later into the underlying submucosa. These authors also drew attention to the absence of clostridia in the substance of the mucosa during the early stages, though later these organisms could be seen lying deeply in the necrotic tissues.

In the freshly examined carcases of sheep suffering from "infectious enterotoxæmia", from whose gut contents *Cl. welchii* type D could be recovered, Bennetts (1932) found that the small intestine showed little more than congestion of its mucosa, though the distal parts of the villi were often hæmorrhagic.

Since morphological studies on animals dying from all these three diseases pointed to an intoxication of enteric origin rather than to some tissue infection as the primary event, several investigators have pursued the problem by determining the toxicity of intestinal contents from affected animals. From this material, suitably pressed, filtered or centrifuged to remove particulate matter, sterile filtrates were obtained for inoculation into mice and other susceptible animals. Montgomerie and Rowlands (1933, 1934) in 1934 described the preparation of filtrates from gut contents in "lamb dysentery" which proved highly toxic for mice when injected intravenously. McEwen and Roberts (1934*b*) had previously described similar toxic filtrates made from sheep dying from "struck" on the Romney Marshes, which were lethal on intravenous injection into rabbits. Gilbert (1934), working in Palestine, prepared a filtrate from the gut contents of sheep dying from "infectious enterotoxæmia" which

killed young rats on intravenous injection, and whose lethal action could be prevented by prior mixture with both types B and D antitoxins, but not with type A antitoxin. Gill (1933) had extracted a toxic component from intestinal contents of lambs dying in New Zealand from "infectious enterotoxæmia", and found that this was poisonous for lambs on intravenous injection. These and other similar studies on this group of clostridial diseases of sheep have thus shown firstly, that some toxic material is produced in the contents of the intestines, probably in those of the ileum, and secondly, that these toxic agents can sometimes be specifically neutralized by antitoxins prepared against filtrates from those known types of *Cl. welchii* which are themselves recoverable from such diseased animals. The inference seems justifiable that the primary pathology in these three diseases of sheep is the ingestion of grass from pastures that have become contaminated with unusual types of *Cl. welchii*, followed by the injury of the exposed mucosal cells by the toxic products that these bacteria liberate in the digesting intestinal contents.

A very important advance was made in the elucidation of these enteric intoxications when Glenny and his colleagues (1933) identified a series of specific antigenic constituents, some of them highly toxic, in culture filtrates of *Cl. welchii* types B, C, and D. These toxins, which they denominated α, β, γ, δ and ϵ toxins, all had noxious properties and were all capable of neutralization by specific antitoxins. Since this pioneer study, other antigenic constituents of such filtrates have been described by McClean *et al.* (1943), Oakley *et al.* (1946), and others, some of which, notably hyaluronidase and collagenase (α-toxin), are enzymes that act on specific tissue substrates.

The toxins described by Glenny, Oakley and others were identified in cultures of the various types of *Cl. welchii* grown *in vitro*; it is now desirable to consider the evidence for their individual occurrence in the intestinal contents of diseased animals, and the possibility that they participate in evoking the lesions just discussed.

There are several reasons for believing that the α-toxin, which plays so large a part in the pathogenesis of clostridial myositis, takes a subordinate role in these enteric intoxications. In the first place, the four types, B, C, D and F, which are known to produce acute enteritis in man and certain herbivora, form comparatively little of the α-toxin on culture, much less than most of the pathogenic strains of type A recoverable from wound infections in man. In the second place, as Dalling (1932) showed early in his studies on "lamb dysentery", antitoxins made with type A strains, and which are effective in human "gas gangrene", are of little avail in type B enteritis ("lamb dysentery") of sheep. This inadequacy of type A antitoxin has been found by later workers to hold also for "struck" and "infectious enterotoxæmia". In the third place, it seems unlikely that this potent lecithinase, which becomes so rapidly fixed to its substrate, would long remain free to exert its toxic action on the mucosal cells when liberated into a medium, such as the gut contents, which contains so much free lecithin.

On the other hand, there are grounds for regarding both the β- and ϵ-toxins as major elements in the enteric intoxications, and much interest centres round attempts to evaluate their relative participation in particular outbreaks. The important part taken by the β-toxin is demonstrable from the observations of Montgomerie and Rowlands (1934) in their study of the toxicity for mice of filtrates made from intestinal contents of animals that suffered from "lamb dysentery" during the 1931, 1932 and 1933 seasons. In the 1932 season, these filtrates could be neutralized by antitoxins made against both types B and C; during the 1933 season, however, type C antiserum failed to protect the mice, but type B and type D antiserum, which had by then become available, were both effective. By comparison with Glenny's analysis of the various kinds of toxin produced by the different types of *Cl. welchii* (*see* Oakley, 1943), this difference could be accounted for by an infection in the earlier years with a type B organism which was forming much β- but little or no ϵ-toxin, while in 1933 the causative organism was forming both β- and ϵ-toxins. Whether this resulted from a change in the strain of the organism that was responsible for the epizootic in the last year, or whether it depended upon some extraneous circumstance that facilitated the formation of ϵ-toxin during that lambing season, it is not possible to say. It seems unlikely that some variant type B strain can have become so widely distributed in the pasturage in so short a time; it seems more probable that some modification in the herbage that year resulted in a chyme that was more favourable to the formation of ϵ-toxin.

The significance of β-toxin in enteric intoxications is further attested by recent experience with necrotizing enteritis in human beings. The organisms that were recovered from a number of such cases in northern Germany since the end of the war have characteristics which differentiate them from other known types of *Cl. welchii*, and which have led to their denomination as type F (Zeissler, 1949). This type has been found by Oakley (1949) to form β-toxin actively on culture, but no ϵ-toxin. Although not conclusive, this is strong presumptive evidence that the ϵ-toxin is not participating in the intoxication of this natural infection in man.

The importance of the ε-toxin in this group of diseases of sheep is not easy to evaluate. That it is a potent necrotizing agent is certain; what is less clear is the extent to which it is produced in the gut contents during natural infections, for this toxin is not only formed more slowly by the organisms themselves, as Miss Ross has pointed out, but it requires some activating agent to evoke its full toxicity. This latter point is of much interest in the pathogenesis of enteric intoxications, because it shows that other factors than mere ingestion of a potentially pathogenic bacterium may be needed for disease to occur. In 1934, Bosworth and Glover made the important observation that the lethality of toxic filtrates of type D cultures was increased many fold by contact with intestinal contents of normal sheep. If the latter had been obtained from sheep whose pancreatic duct had been previously ligated, however, this exaltation in toxicity did not take place. From these and other experiments, they concluded that the activation was brought about by trypsin, and this conclusion has since been confirmed and extended by Turner and Rodwell (1943) in Australia. It seems, therefore, that the ε-toxin is liberated by the bacteria in the form of a "prototoxin"—a material of relatively low toxicity itself, but which, if acted upon by proteolytic enzymes derived from host or other bacteria, is converted into the much more potent form in which it appears to act.

From the information at present available, it seems likely that in all forms of *Cl. welchii* enteritis, both of man and sheep, the β-toxin is the main intoxicating agent, especially in the earlier stages of the disease. In some outbreaks, brought about by types B or D, the ε-toxin may be produced as well, and in such instances the severity of the intoxication is increased and its clinical character changed.

I shall turn now to an important, but still obscure, point in the pathogenesis of these intoxications—the extent to which the actual toxins gain access to the circulating blood and produce what may be properly termed a "toxæmia". The need for the identification of the toxin in the blood before a toxæmia can be assumed is often overlooked, and clinical manifestations associated with other organs than those primarily involved are often mistakenly attributed to a general dissemination of the toxin when really they are due to non-specific secondary disturbances such as fat embolism or dehydration. In clostridial myositis caused by type A organisms, although the whole body appears to be intoxicated, search for the α-toxin in the circulating blood has so far failed to disclose its presence either in naturally occurring "gas gangrene" in man or in experimental infections in animals (Cooke *et al.*, 1945; MacLennan and Macfarlane, 1945; Zamecnik, Nathanson and Aub, 1947). It seems likely that the rapid fixation of this toxin to its substrate lecithin, which is present in large amounts in all tissues, limits its spread from the site of its liberation and thereby prevents a toxæmia. So far, there seems to have been no attempt made to identify, by specific antitoxin neutralization methods, the presence of either β- or ε-toxin in the blood of affected sheep, though such a demonstration is necessary before a toxæmia in clostridial enteritis can be regarded as other than inferential. There is, however, some less direct evidence that favours the belief that the ε-toxin at least enters the circulating blood. In some instances of type D "infectious enterotoxæmia", the syndrome is complicated by disturbances in the kidneys and central nervous system. The condition known as "pulpy kidney" is now known to be a sequel to infection with this type of *Cl. welchii*; that the renal lesion depends upon a concurrent toxæmia is rendered probable by the fact that degenerations in the convoluted tubules indistinguishable from those in the naturally occurring disease have been produced experimentally by the intravenous injection of toxic filtrates (Montgomerie and Rowlands, 1934; Oxer, 1932). Similarly, in the acute forms of the "infectious enterotoxæmia" of sheep due to type D infections, the terminal stages are often dominated by severe neurological disorders. Oxer (1932) has described loss of power of the limbs, convulsive symptoms with violent galloping movements as late manifestations in natural infections. These symptoms have been reproduced by Kellaway and his colleagues (1940) by intravenous injections of toxic filtrates from type D organisms, and, by further analysis, they attributed the disorder to the direct action of the toxin at some level intermediate between the cerebral cortex and the spinal cord. The reproduction of these two important features of the natural disease by means of an intravenous injection of specific toxic filtrates is substantial evidence that the enteritis of "infectious enterotoxæmia" may be succeeded by a true toxæmia in which the ε-toxin becomes distributed throughout the body.

I shall conclude by drawing attention very briefly to an aspect of bacterial intoxication which has received too little consideration—the possible dependence of the clinical syndromes on such secondary features as hæmoconcentration, fat embolism and the superadded toxic actions of products of injured tissues. Gordon and his colleagues have initiated such a line of enquiry by studying the biochemical and hæmatological effects of the intravenous injection of toxic filtrates of *Cl. welchii* types A, C and D into sheep (Gordon *et al.*, 1940). Their major findings were the acute hæmolytic anæmia which followed injection of type A toxin, and the hæmoconcentration which followed type D toxin. It would be interesting to know whether this latter disorder—which has also been noted by Kellaway—also develops in the naturally

occurring "infectious enterotoxæmia" of sheep. Some similar hæmoconcentration must almost certainly take place in "lamb dysentery" with its profuse intestinal discharges, and—as with cholera in man—it might prove amenable to measures directed to maintaining blood volume and serum electrolyte balance.

It has long been suspected that the release of toxic substances from injured tissues contributes to the syndromes of bacterial intoxications, but it is only recently that the problem has been subjected to careful analysis on pharmacological lines. This work has been mainly carried out by Kellaway and his associates at Melbourne on various clostridial toxins, and it is not possible to do more than allude briefly to these observations here. It seems, however, that in consequence of differences in their content of the various specific toxins described by Glenny, the toxic filtrates of the four main types of *Cl. welchii* differ in their ability to release pharmacologically active substances from the tissues—filtrates from all four types cause the liberation of adenyl compounds, but only those of types B and D bring about the release of histamine from perfused organs. There seems to be some connexion between the presence of α-toxin and adenyl compounds and between ε-toxin and histamine (Kellaway and Trethewie, 1941).

It will probably be through correlations of such pharmacological assays with the functional and structural disturbances occurring in these clostridial infections that a rational interpretation of the signs and symptoms will eventually emerge. In the meantime, however, the investigation of the disordered physiology in both naturally diseased and experimentally intoxicated animals would prove rewarding, not only for its academic interest, but also for the construction of a more logical foundation for treatment.

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Dr. M. G. Macfarlane (*Lister Institute*): Culture filtrates from *Cl. welchii*, *Cl. œdematiens* type A and *Cl. œdematiens* type B have been shown to contain lecithinases which are similar in biochemical action but immunologically distinct. Following up the observation of Oakley, Warrack and Clarke (1947) that these lecithinases differ in their capacity to hæmolyse red blood cells from different species of animals, the rate of hydrolysis of the phospholipin in intact cells by equal quantities (enzyme units) of the different lecithinases has been studied, and remarkable differences found. Thus, with one enzyme unit acting on 2 ml. of cells, the phospholipin of sheep cells is hardly hydrolysed by *Cl. œdematiens* γ-lecithinase, but rapidly hydrolysed by *Cl. welchii* lecithinase, while the phospholipin of horse cells is rapidly hydrolysed by the *Cl. œdematiens* enzyme and slowly by the *Cl. welchii* enzyme. If the phospholipin is extracted from sheep cells and made into an aqueous emulsion it is attacked equally rapidly by the *Cl. welchii* and *Cl. œdematiens* enzymes (Macfarlane, 1950). The rate of hydrolysis in the intact cell therefore appears to depend on the "goodness of fit" between the particular cell surface and the particular lecithinase, which clearly, from their immunological specificities, do vary in structure. This "goodness of fit", which can apparently determine the actual rate of attack of an inherently toxic agent upon an inherently susceptible cell, would appear to be a basic factor determining the virulence of a particular parasite in a particular host.

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Dr. W. S. Gordon (*Agricultural Research Council, Field Station, Compton, Berks*): Dr. Oakley, with his wealth of experience and exact knowledge in the study of anaerobes, has opened this Discussion in a refreshingly acceptable but provocative manner.

I know he will agree, however, that while anaerobes may only infrequently be the primary cause of disease, these organisms or their toxins are frequently the cause of death and, further, in certain diseases of animals, for example, lamb dysentery caused by *Cl. welchii*, type B, vaccines and sera have been shown conclusively to have a very high efficiency in protecting lambs against death from this condition.

With regard to the so-called enterotoxæmias, I am beginning to doubt if the detection of an anaerobic toxin in the contents of a small intestine is proof that this toxin must have been the cause of death. My reason for doubt is the fact that when a number of lambs die suddenly in a flock under circumstances that suggest enterotoxæmia, one may find some lambs with detectable toxin in the gut contents and others, with the same history and post-mortem picture, which have no detectable toxin in the gut. Similarly, in grass sickness in horses, a disease characterized by complete bowel stasis, an acute anhydræmia and death from a shock type of reaction with circulatory failure, one may find the toxin of *Cl. welchii*, type D, in the intestinal contents of 2 or 3% of acute cases. At one time I thought it possible that the toxin of *Cl. welchii*, type D, might be the cause of death in this disease. It has subsequently been shown, however, that 1,000 horses immunized against this toxin were as readily susceptible to grass sickness as 1,000 control horses grazed under the same conditions. After that experiment I have concluded that in grass sickness there is a factor, still unknown, which causes bowel stasis. If an animal in this condition has been grazing a pasture where *Cl. welchii*, type D, is present, it is probable that this organism has gained access to the digestive tract. In such cases when the bowel becomes static, it provides conditions suitable for the organism to multiply and form toxin in the gut contents. This toxin, however, does not appear to be the cause of death, nor does its presence in the bowel appear to have any significance in the causation of the disease, hence my scepticism in accepting present evidence as conclusive that enterotoxæmia is a specific disease entity due to the absorption of anaerobic toxins from the intestine.

Dr. W. E. van Heyningen (*Sir William Dunn School of Pathology, Oxford University*): Llewellyn Smith (1942–43) showed that different samples of tetanus toxin which were equipotent in their toxicity to guinea-pigs differed considerably in their toxicity to rabbits. This phenomenon may be related to Miles and Miles' finding (1950) that samples of toxin from different strains of *Cl. bifermentans* which were equipotent in their *in vitro* lecithinase activity differed considerably in their toxicity to mice. This kind of phenomenon has not yet been thoroughly investigated and is probably widespread. It is conceivable that the difference in virulence of the three strains of *C. diphtheriæ* might originate from analogous differences in their toxins. Samples of toxin from different strains of the same organism, or even different samples of toxin from the same strain, may differ in their toxicity to a given animal per unit weight of pure toxin, or per unit of some *in vitro* or *in vivo* activity (such as toxicity to another animal). Toxins which bring about the same fundamental reaction and which are neutralized by the same antitoxin may still differ quantitatively, and possibly qualitatively, in their action in the animal if they differ in some property, like molecular weight or electric charge, which affects their ability to make contact with their substrates in the animal body. The fact that different lecithinases differ in their toxicity per unit of lecithinase activity need not cast doubt on the suggestion that their toxicity is due to their lecithinase activity. The degree of toxicity may be affected by factors other than the nature of the active centres.

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Clinical Section

President—W. A. BOURNE, M.D.

[*April* 14, 1950]

MEETING HELD AT THE ROYAL SUSSEX COUNTY HOSPITAL, BRIGHTON

Pericardial Talc Insufflation (Four Cases).—E. W. LINDECK, M.R.C.P., for W. A. BOURNE, M.D.

Case I.—Female aged 54. Admitted to hospital after several months' confinement to bed with dyspnœa, œdema and chest pain. Weight 15 st. 3 lb. (96·7 kilo.); orthopnœic with slight ankle œdema; B.P. 130/70; E.C.G., left bundle branch block. Several weeks of inpatient treatment by weight reduction, neptal, priscol and procaine intercostal block did not relieve pain. Talc insufflation by Mr. Forrester Wood on March 15, 1949. Discharged from hospital March 31. Has improved symptomatically to a considerable degree and spent several days last summer on the beach in charge of her grandchildren. E.C.G. shows no change.

Case II.—Female aged 48. 1947, admitted to hospital with a few weeks' history of exertional chest pain: immediately after admission developed cardiac infarction (shown electrocardiographically). Discharged with electrocardiographic recovery but persistent exertional pain resisting routine measures. E.C.G. while under observation developed R-T depression in leads I, II, and V4. Talc insufflation by Mr. Forrester Wood on March 31, 1949. Pericardial friction later developed and E.C.G. showed inversion of T waves in all standard leads, unipolar chest leads and aVF. Two months later exertional pain was diminished but non-exertional left axillary pain was severe. This improved four months after operation, when exertional pain was returning and the E.C.G. showed recovery of T waves to positive. There is now considerably less pain than before operation.

Case III.—Female aged 53. Seen as outpatient November 1948 with substernal exertional pain of two years' duration and dyspepsia. E.C.G. showed left bundle branch block. Barium meal: gastric ulcer. Medical treatment relieved dyspeptic symptoms but exertional pain persisted after six months' routine therapy. Talc insufflation by Mr. Forrester Wood on May 23, 1949. Discharged one month later. Pain has been considerably relieved but dyspnœa persists and exertion is limited. E.C.G. shows no change.

Case IV.—Female aged 65. Admitted to hospital with some years' history of disabling exertional pain and suspected infarction in March 1949. Obese; no congestive failure. B.P. 180/100. E.C.G. physiological. Intercostal block did not relieve symptoms. Talc insufflation by Mr. K. Powell on December 9, 1949, with resection of left fifth costal cartilage. Pleurisy developed post-operatively. E.C.G. showed no change. Discharged from hospital January 17, 1950. Considerable symptomatic relief.

Comment.—This procedure was suggested as a measure of desperation in Case I. Her unexpected toleration of it caused it to be tried in three other apparently resistive cases regarded as having cardiac pain. The general method was based on Thompson's procedure (1948), but a variation devised by Mr. Forrester Wood without any costal cartilage or rib resection was used in 3 cases. There was no real anxiety post-operatively although 3 cases had abnormal E.C.G. records, 2 with bundle branch block and 1 suggesting coronary ischæmia. All the patients state that the severe exertional pain is considerably relieved and regard the operation as having been worth while. Their capacity for exertion is not increased except in Case I. There is no significant electrocardiographic change.

A theoretical basis has since been suggested in Harrison and Wood's article (1949), in which bridging of a coronary gap by pericardial vessels is illustrated. The operation was,

however, tried quite empirically. It has been performed safely and the patients state their pain is less.

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Dr. A. Schott thought that in the 4 patients the diagnosis of angina pectoris could be considered established; the sudden onset of symptoms in 3 of them suggested the possibility of a coronary occlusion as initiating factor. In 1 of the patients the increase in exercise tolerance was impressive, in the remaining 3 the improvement was encouraging though the time of observation and the amount of exertion so far attempted after operation were inadequate for forming a more definite opinion. In cases with bundle branch block an electrocardiographic follow-up did not help in assessing improvement. In view of the agonizing distress of some patients with angina pectoris any attempt at relief by new methods should be welcomed if all established methods had failed. As the site of myocardial infarction could now be located electrocardiographically with increasing accuracy the point was raised whether the exact site and area of insufflation might not be of importance, in order to encourage the supplementary blood supply as near as possible to the lesion.

Xanthomatous Biliary Cirrhosis.—W. A. BOURNE, M.D., F.R.C.P., and J. K. WAGSTAFF, M.R.C.P.

Mrs. A., aged 56.

In 1945 she noticed a wart-like skin lesion 0·5 cm. in diameter on the right arm. Apart from this she was in good health until March 1948 when she developed a non-specific respiratory infection with a disproportionate degree of asthenia.

In April 1948 she became icteric, and yellowish infiltrations appeared on the eyelids, palms, digital flexures and finger tips; the lesions of the hands were tender. Generalized pruritus and the development of further wart-like swellings under the dorsal skin of the arms caused her to seek medical advice in July 1948. Her appetite was poor and her weight had fallen from 10 st. 4 lb. to 8 st. 8 lb.

Family history.—No other cases of xanthomatosis.

On examination (July 1948).—The skin lesions were typical xanthomata of the plane and tuberous variety. The liver edge extended four fingerbreadths below the costal margin, with a smooth anterior surface; the spleen was also palpable.

Investigations:—

	August 1948	September 1948	October 1948	October 1949
Cholesterol Total	1,266	900	1,600	1,280 mg.%
Cholesterol ester	—	—	30 mg.%	—
Serum bilirubin	2 mg.%	—	—	—
Icterus index	—	—	—	8 units
Thymol turbidity	15	—	—	90 units
Alkaline phosphatase	67	—	—	39 units
Serum albumin	5·4	—	—	4·5 grammes%
Serum globulin	1·4	—	—	3·8 grammes%
Blood urea	40 mg.%	—	—	—

Blood count (October 1949) R.B.C. 4,090,000; Hb 76%; C.I. 0·95; W.B.C. 6,900; normal differential.

X-ray chest: Normal lung markings.

X-ray skull and other bones: Normal appearances.

Biopsy of lesions of the right forearm showed xanthomatosis.

Course up to September 1949. Despite a fair appetite her weight had fallen to 6 st. 3 lb. and there was a generalized deep dusky bluish-brown pigmentation. The xanthomatous lesions had spread to the neck, scapular region and to the buccal mucosa. Her liver had enlarged down to the iliac crest but the spleen was no longer palpable.

Now (March 1950) she has become somewhat drowsy. Xanthomata have appeared over the lower extremities and those on the soles of the feet are very painful.

Comment.—All the diagnostic features of the syndrome according to Thannhauser and MacMahon are fulfilled. (1) Skin xanthomata of the plane and tuberous variety. (2) Enlarged liver and spleen. (3) Obstructive type of jaundice of more than a year's duration. (4) Extremely high serum cholesterol. (5) Low values of neutral fat—the serum being transparent and not creamy.

Unfortunately owing to her very difficult temperament it has not been possible to complete further investigations. Liver biopsy was refused.

The nature of the wart-like lesions that appeared on her right arm in 1945 is uncertain. In this condition the cutaneous xanthomata usually appear with, or some months after, the jaundice.

No observation can be made on the efficacy of a diet free from animal sterols as it seems unlikely she would adhere to it.

By taking biopsies in early cases MacMahon showed that the site of the obstruction was in the smallest bile ducts and that in his cases it was due to a chronic non-specific inflammatory reaction concentrated around these vessels.

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Dr. O. Garrod: With regard to the "honeycomb lungs" which have been reported in association with xanthomatous biliary cirrhosis, 3 cases were reported by Oswald and Parkinson (*Quart. J. Med.*, 1949, **18**, 1). The occurrence of cystic changes in the lungs in xanthomatosis was first discovered by Rowland in 1928 (*Arch. int. Med.*, **42**, 611). Several other cases have also been described.

Recurrent Chondroma of Ribs.—J. R. GRIFFITH, F.R.C.S.

L. S., male, aged 60. A case of chondrosarcoma of the left ribs of twenty-four years' standing. This man had undergone four operations, the third to the sixth ribs being removed from the sternum to the mid-axillary line, together with its pericardial covering. A large amount of invaded lung had also been removed. The heart was left unprotected by the ribs.

Histological diagnosis of malignant disease was first made in June 1936.

Present condition.—He has a recurrence, which is widely involving the lung, and appears to be irremovable. It has been decided to let the disease take its course.

POSTSCRIPT 1.12.50.—This man is still carrying on with his business. The recurrent tumour is however now adherent to the heart. J.R.G.

Idiopathic Steatorrhœa.—C. BARRINGTON PROWSE, M.R.C.P.

L. L., male aged 53.

History.—October 1948: Consulted private doctor because of weakness and loss of weight.

December 1948: Not having responded to treatment with iron and tonics admitted to Royal Sussex County Hospital for investigation. Complained of frequent loose pale stools, weakness, failing vision and "cramps" in the hands.

Past and family history not relevant.

On examination.—Pale, ill, wasted. Abdomen distended and tympanitic. Chvostek's and Trousseau's signs positive; carpopedal spasms noted. Impaired resonance and breath sounds with persistent rhonchi at both lung bases especially the right.

Investigations revealed soft bulky greyish white stools containing 68% split and 32% unsplit fat; histamine-fast achlorhydria; hyperchromic anæmia (R.B.C. 2,900,000; Hb 75%; C.I. 1·29; W.B.C. 26,000); plasma proteins (6·4%); low serum calcium (4·8 mg.%); low flat glucose tolerance curve; suggestive evidence of basal bronchiectasis more marked on right side on straight X-ray; sputum negative for T.B.

Progress.—Made slow but steady progress under treatment with vitamins A, D, B_1 and B_2, folic acid, anahæmin, calcium lactate and gluconate, hydrochloric acid and pepsin, high protein, low fat diet.

February 1949: Discharged from hospital relieved of the calcium deficiency and anæmia (R.B.C. 4,070,000; Hb 90%; C.I. 1·12; W.B.C. 13,700) and passing one stool a day, still pale and rather bulky.

January 20, 1950: Readmitted to hospital. Pale, thin, weak and eyesight again failing. Having daily attacks of tetany. Tongue smooth, nails flattened, Trousseau's sign positive. Anæmic (R.B.C. 3,220,000; Hb 60%) C.I. 0·94; W.B.C. 12,800). Serum calcium and serum protein low (5·0 mg.% and 5·3% respectively).

Progress.—Little response to treatment. Gradually increasing œdema of arms, legs and trunk. Development of ascites and hydrothorax and seborrhœic type of dermatitis.

Additional treatment.—Transfusion of 2 pints packed cells, high potency Ostelin 50,000 units daily. Casinal. General condition improved slowly—but œdema remained unchanged until a dramatic diuresis followed the exhibition of Neptal.

March 20, 1950: Discharged from hospital without œdema and having serum protein of 6·3%, serum calcium of 7·8 mg.% and a blood count of R.B.C. 4,520,000; Hb 84%; C.I. 0·93; W.B.C. 8,400. Passing one pale but formed stool daily.

Comment.—Several features of this case are worthy of particular notice: (1) The absence of diarrhœa as an initial symptom. This points to the importance of considering steatorrhœa in the differential diagnosis of cases of chronic and resistant anæmia.

(2) The early appearance of calcium deficiency in spite of the absence of diarrhœa. This suggests a failure to absorb calcium rather than a tendency to re-excrete it.

(3) The resistance of the anæmia to treatment, its ready tendency to relapse, and the failure of treatment completely to correct the steatorrhœa even when other symptoms have been relieved.

This serves to emphasize the inefficiency of the treatments at present in use, which only overcome defective bowel absorption by the presentation of essential elements in excess.

(4) The possible significance of chronic pulmonary sepsis in the ætiology of the disease.

Dr. Alastair Anderson: The importance of steatorrhœa lies in the frequency with which it is occult, gross disorders of hæmopoiesis and/or calcium phosphorus metabolism developing without any symptomatic disturbance of bowel function. Furthermore, even if attention is directed to intestinal fat absorption, it is commonly only practicable to have quantitative estimations of the dried fæcal fat content, expressed as a percentage of an imponderable unabsorbed fæcal residue and under these circumstances the existence of significant steatorrhœa may be overlooked. Fat balance studies are essential in the investigation of these cases. Ætiologically the diagnosis lies between "idiopathic" steatorrhœa, probably frequently associated with cœliac disease in the same patient in earlier life, and chronic pancreatitis. While the flat glucose tolerance curve in this case supports the former, it would be worth while to estimate the trypsin activity of aspirated pancreatic secretion.

It is fortunate that this patient's negative calcium balance manifested itself by tetany—there having been presumably no compensatory parathyroid hyperplasia. The carpopedal spasms drew attention to a gross disturbance of calcium-phosphorus metabolism which might otherwise have passed undetected until osteomalacia had developed.

Dr. O. Garrod: Five cases of iron deficiency anæmia which did not respond to large doses of oral iron but only to intravenous iron (Ferrivenin) were reported at a meeting of the Medical Research Society in February of this year, (Hawkins, C. F., Peeney, A. L. P., and Cooke, W. T., 1950, *Lancet*, ii, 387) and were found to have steatorrhœa. I have recently seen a similar case of iron deficiency anæmia that has now developed tetany (serum calcium 6 mg.%). We are about to investigate her more fully as we feel that she has almost certainly got steatorrhœa.

POSTSCRIPT.—Idiopathic steatorrhœa confirmed. Excellent response to Ferrivenin. Red blood cells became macrocytic.—O. G.

Sarcoidosis.—G. M. WAUCHOPE, F.R.C.P.

Mrs. B., aged 48.

Admitted for myomectomy and appendicectomy. Hands and feet observed to be characteristic of sarcoidosis. The condition is chronic and apparently painless in this case.

Areas affected: Hands, feet, nose, lungs.

No deposits found in other systems.

W.R. negative.



FIG. 1.



FIG. 2.

The diagnosis of sarcoidosis depends primarily on the histological findings.

In the present case the appearance of the skin lesions is characteristic, the nose, fingers and toes being affected (Fig. 1).

The X-rays of the hands and feet show the "shot-hole" cystic areas in the heads of the phalanges, the third left and fourth right terminal phalanges of the hands have almost disappeared (Fig. 2).

The lungs show bilateral enlargement of the hilar glands with characteristic diffuse mottling of both lungs.

The reaction was positive to 0·005 mg. of Old Tuberculin.

The patient has no complaints and no treatment has so far been given.

POSTSCRIPT (December 1950).—Physiotherapy (heat and massage) has improved the colour and temperature of the hands: calcium with vitamin D is being given.

Failure in Congenital Heart Disease with Left to Right Shunt. Five Cases.—R. KEMBALL PRICE, M.D.

H. M., male, aged 37. Atrial septal defect.

History.—Heart disease diagnosed soon after birth. Never attended school. At 14 started work, cycling 15 miles to it daily, and continued working. Has had four attacks of "pneumonia". Four years ago (age 33) began attacks of rapid palpitation with blueness.

Three years ago (age 34) began to become short of breath, and six months later abdomen and legs became swollen. Has spent long periods in bed since but gets about.

Examination.—Dyspnœa at rest. Slight cyanosis. Heart enlarged with loud systolic murmur and early diastolic murmur to left of sternum. B.P. 135/90. Electrocardiogram (Fig. 1): Right

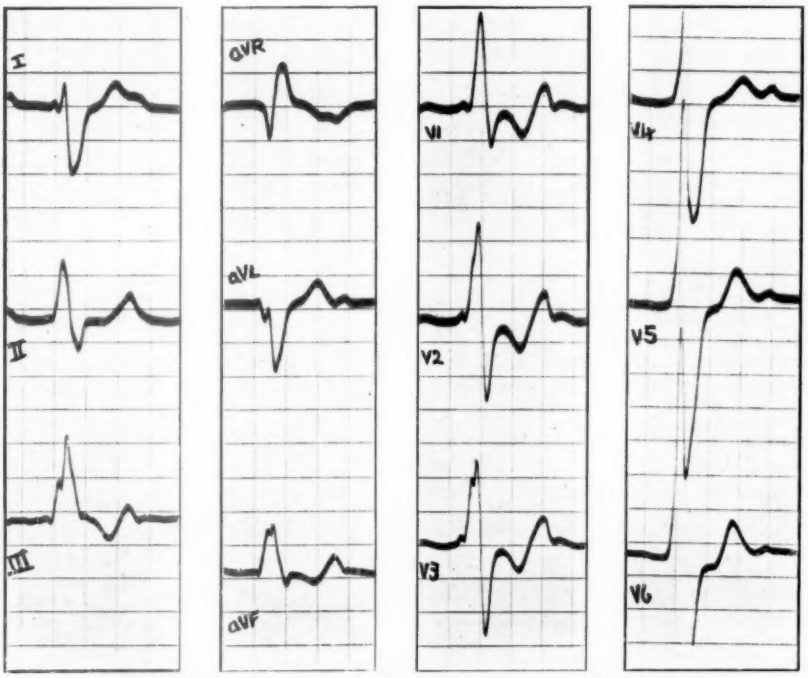


FIG. 1.—Electrocardiogram—A.S.D. showing right bundle branch block.

bundle branch block. Cardioscopy: Considerable general cardiac enlargement with much prominence of pulmonary vessels with striking pulsation.

Comment.—Heart failure in this condition is unusual before adult life, though records of a girl who failed rapidly and died at the age of 14 were shown. The remaining 3 patients, one of whom had mitral stenosis as well as atrial septal defect (Lutembacher's syndrome) showed signs of failure when in their thirties. All had considerable cardiac enlargement with splitting of the first heart sound at the apex and of the second sound in the pulmonary area, and pulmonary diastolic murmurs. The blood pressure was normal in all. The electrocardiogram showed right bundle branch block which is present in partial or complete form in over 90% of such cases and has a diagnostic significance. Most characteristic is the radiological picture which shows great enlargement of the pulmonary artery and its branches with

pulsation extending out into the lung fields. The left auricle, except with associated mitral stenosis, shows little or no enlargement (Fig. 2). Two of the patients had symptoms suggestive of paroxysmal tachycardia, and one who was electrocardiographed during an attack showed auricular flutter with 1:1 rhythm and later with 3:1 A.V. block. After years of breathlessness enlargement of the liver appeared and later œdema of the legs. It is possible that the repeated attacks of "pneumonia" of which so many of these patients tell may in fact be congestion of the pulmonary circulation due to the left to right shunt.

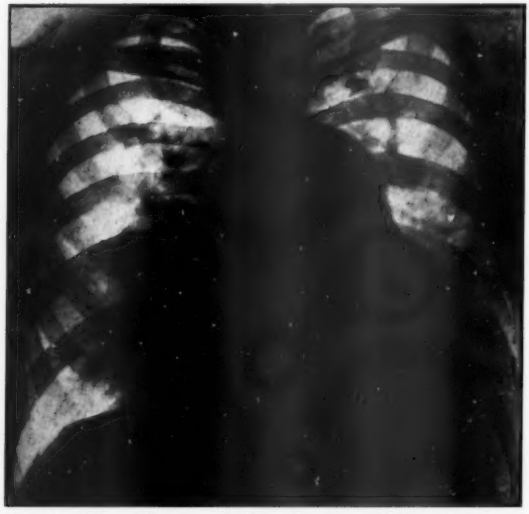


FIG. 2.—Teleradiogram—A.S.D. showing cardiac enlargement and enlarged pulmonary arteries with pulmonary plethora.

In contrast, a woman of 57 with a patent ductus arteriosus had been diagnosed as suffering from aortic incompetence. The large pulmonary artery on cardioscopy and the continuous murmur in the pulmonary area with diastolic accentuation indicated the correct diagnosis. In her case the electrocardiogram was normal. B.P. 170/60, and the pulmonary branches were less prominent.

Hæmorrhagic Diathesis.—H. G. McGREGOR, M.D., and S. L. KAYE, M.D.

Miss E. L., aged 29.

Previous and family history not significant.

History of present illness.—The symptoms could be arranged as follows:

Onset of excessive menstrual bleeding in 1942, followed by lengthening of the periods and dysmenorrhœa, i.e. pain and aching in the right iliac area. This was treated by D. and C. which reduced the menorrhagia for one year. A relapse was treated by ventri-suspension of the uterus. The operation produced no benefit and her symptoms remained as described except for two remissions lasting about four to six months during the next four years, that is until the present time.

In 1948 bruises began to appear on the limbs, and occasionally over the buttocks. These bruises start as a tender red area which becomes discoloured in the normal manner of a bruise, and then gradually fade with slow disappearance of the discoloration due to the blood pigments. The bruise is excessively tender.

Pain in the right iliac area tending to radiate into the thigh and across the lower abdomen. This symptom is worse in association with episodes of heavy bleeding.

Investigations.—Clinical examination apart from the presence of the bruises described above is negative. Tenderness most marked in the right iliac fossa is a constant finding. No abnormality has been felt on vaginal examination and three consulting gynæcologists, though admitting the presence of severe pain, state it is not ovarian in origin but are unable to locate its site.

Pathological findings.—W.R. and Kahn negative. R.B.C. count has varied between 3,200,000 and 4,070,000. Hb 11·15 grammes %. C.I. 1·0. Reticulocytes 0·6%. Hæmatocrit 35%. W.B.C. 6,700. Differential normal. Platelets 260,000–350,000.

Clotting time, bleeding time, clot retraction were within normal limits.
Liver functions: tests normal.
Blood calcium, blood fibrinogen, normal.

Treatment.—Blood transfusions, iron, Rutin, vitamins including ascorbic acid, Anthisan, Antistin have had no curative effect. She was presented to the Clinical Section and the following suggestions considered:

(1) Emotional menorrhagia: investigated and excluded.
(2) Self-induced bruises: excluded after careful consideration.
(3) Telangiectasia: no evidence to support the diagnosis on clinical grounds.
(4) Hæmophilia, purpura or other blood disease including the leukæmias: no supporting evidence.

Follow up.—Treatment has been continued by Dr. S. L. Kaye on the following basis:

(1) That the menorrhagia is of endocrine origin, probably ovarian and the pain is related in some way to the ovary or to bleeding between its peritoneal coats.

(2) The "bruising" is secondary to the long-continued hæmorrhage resulting in "capillary oozing". This was the explanation thought most likely when the case was discussed with Dr. Parkes Weber.

Testosterone 25 mg. by injection twice weekly. This appeared to give excellent results at first but then was abandoned because of troublesome acne.

Ethisterone mg. 10, Ethinyl œstradiol 0·03 mg. daily for sixteen days in an arbitrary cycle. This also appeared to produce non-bleeding intervals and it was hoped that the menorrhagia would gradually diminish and the normal period re-establish itself. However, the patient recently suffered a fall and up to the time of writing has been confined to bed with flooding and severe right iliac fossa pain.

Future plan.—It is proposed to perform a dilatation and curettage of uterus; if this produces no significant findings or benefit then a laparotomy, and if no abnormality can be found in the pelvis, to proceed with a hysterectomy.

Scleroderma and Sclerodactylia: Treatment with Foam Baths.—R. W. WINDLE, M.D., D.Phys.Med.

Mrs. B., aged 38. Married. One child aged 6.

Worked in a laundry from the age of 14, and was employed on hand ironing. At the age of 22, when the weather was cold there was occasional deadness and numbness at the tip of the third finger of the left hand. A year later all the fingers of the left hand were involved. Three years after the changes began in the hands, a similar condition started in the feet. A bilateral cervical sympathectomy was performed in 1947 at Guy's Hospital. The flexion of the fingers gradually increased, and the condition in the feet and legs had become so bad that a lumbar sympathectomy was undertaken in 1948. It was noticed at this time that there was loss of elasticity in the skin of her face. During 1949 stiffness across the chest was also noticed. In January 1950 a course of foam baths was given. After this, she was able to open her mouth with comparative ease (Figs. 1 and 2), and the stiffness in the skin was also markedly improved.



FIG. 1.—Before treatment.



FIG. 2.—After treatment.

Xanthomatous Synovioma.—J. C. F. LLOYD WILLIAMSON, F.R.C.S.

Mrs. M. G., housewife, aged 53.

History of having injured base of left thumb from heavy lifting during the war, and some pain ever since; this probably due to osteo-arthritis of the first metacarpophalangeal joint.

November 1948: History of swelling proximal to the joint. Thought to be a ganglion but somewhat atypical.

29.4.49: Operation (with bloodless field). Dissection of the tumour. Immediately the skin was reflected the tumour was seen to be quite unlike a ganglion but solid and greyish yellow in colour and deeply grooved by the abductor pollicis longus and the extensor pollicis brevis; it was considered probably to be a xanthoma.

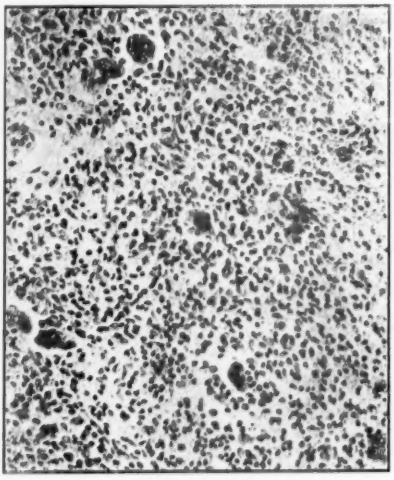


FIG. 1.—x 170.

Pathological report by Dr. R. W. P. Johnson: "A pseudo-xanthoma of the tendon sheath."

"This is a giant-cell tumour arising from a tendon sheath. These tumours have in the past been given many different names, most of which are quite inappropriate; for example they have been called "myelomas" or "myeloid tumours" although they have no connexion whatever with myeloid tissue. "Giant-cell tumour" is also an unsatisfactory term as the tumours do not invariably contain giant cells. It is now known that these tumours arise from the synovial cells of a tendon sheath and the correct designation is therefore synovioma. The synovial cells are thought to be modified fibroblasts.

Occasionally, as in this case, the tumours have a yellowish colour due to the presence of lipoid material in the tumour cells; the name xanthoma has been applied to this type of tumour, but this is also a misleading term, as true xanthomata are found in certain diseases of fat metabolism. The present tumour should therefore be called a xanthomatous synovioma. It is benign, but there is a possibility of recurrence if the surgical removal was incomplete."

April 1950: Remains satisfactory.

This case might also be termed "Synovioma of Tendon Sheath".

Congenital Arteriovenous Aneurysm.—W. R. FORRESTER WOOD, F.R.C.S.

Mrs. E. P., aged 61. Housewife.

History.—At about the age of 8 an abnormal swelling was first noticed in the left side of the neck. This has gradually and slowly increased in size ever since, and has recently spread to the pre-auricular area (Fig. 1). It gives rise to very few symptoms—mainly difficulty in using the telephone—left-sided headaches and discomfort on pressure on the left side of the neck.

Past history.—1938: Hysterectomy and oophorectomy. 1940: Cholecystectomy.

Examination shows a well-marked arteriovenous aneurysm on the left side of the neck. B.P. 170/96 on 8.2.50. X-rays of skull and chest negative. X-ray of cervical spine shows pressure erosion of transverse processes on the left side. W.R. negative. No glycosuria.

Mr. Rex Lawrie: I am doubtful if the symptoms or prognosis justify operation. If it is necessary to ligate a main carotid artery to control the fistula, it is usually considered safe to do so if no hemiparesis occurs within forty-five minutes of applying a temporary clamp to the vessel under local anæsthesia.



FIG. 1.—Arteriovenous aneurysm of the left side of the neck extending from the clavicle to the pre-auricular area.

(Mr. Forrester Wood's case p. 900)

Traumatic Aneurysm of Popliteal Artery.—D. P. KENNEDY, F.R.C.S.I.

Male, aged 70.

History.—Slipped downstairs five days prior to admission on 11.1.50.

Examination.—Ill, febrile patient. B.P. 215/150. Severe pain and limitation of movements left knee-joint. Whole joint appeared diffusely swollen and tender—? suppurative arthritis.



FIG. 1.—Pre-ligation.



FIG. 2.—Post-ligation.

Aspiration: 100 c.c. of cloudy fluid. Culture: sterile. The joint was put at rest on a back splint of plaster of Paris and chemotherapy commenced.

Fourteen days after admission, gross œdema of the whole leg was observed, and a pulsating swelling in the popliteal fossa was noted.

Arteriogram shows very poor collateral circulation (Fig. 1).

Proximal ligature was performed on 10.2.50—approximately one month after injury. Artery noted to be very hard.

The patient's severe pain was promptly relieved. A gangrenous patch, the size of a five-shilling piece, developed on the heel; the gangrene remained localized and dry.

A further arteriogram was done three months after ligation (*see* Fig. 2).

The patient has now left hospital and is walking well on crutches. The heel slough is slowly separating and when this is complete I hope he will be able to bear weight on the affected leg.

The interesting points about this case are: (1) Subcutaneous rupture of the popliteal artery is rare. (2) Gangrene of the limb did not occur—despite the generally poor cardio-vascular system. In most of the cases recorded the diagnosis was not made till the onset of gangrene. (3) A pulsatile swelling and a pulsation murmur were both noted fourteen days after injury. In 34 recorded cases of false or traumatic aneurysm, or what are better described as arterial hæmatomata, pulsation was only twice observed and a murmur only once. (4) The patient refused amputation. I think his limb will eventually be more useful to him than an artificial one.

Gastrectomy with Resection of Pancreas and Spleen for Massive Gastric Ulcer simulating Carcinoma.—H. J. McCURRICH, M.S.

Mrs. R. I., aged 63.

On 16.2.50 complained of anorexia, loss of weight and epigastric discomfort since last August. Had vomited a few times and on one or two occasions had brought up blood.

Palpable mass in the epigastrium to the left of the mid-line.

Mild hæmatemesis on 27.2.50. A test meal before admission showed a slight excess of acid.

Diagnosis.—Carcinoma of the stomach. Her hæmoglobin was 64% and R.B.C. 3,490,000. At operation a large indurated mass on the posterior surface of the stomach invading the pancreas was discovered. The stomach, body and tail of the pancreas and spleen were removed, no enlarged glands or metastases were seen. The duodenum was found dilated to a transverse width of 2 inches. The stomach was divided an inch below the œsophagus and the duodenum anastomosed to the small cuff of stomach below the œsophagus (Billroth I method). Four pints of blood given after operation.

On	2.3.50 (day after operation)	blood sugar was	197	mg.%.
	4.3.50	,, ,, ,,	126	,,
	15.3.50	,, ,, ,,	85	,,

The glucose tolerance test showed the usual rapid rise after a gastrectomy but slower fall than usual.

There was an ulcer on the posterior surface of the stomach. The diameter of the ulcer was 5 cm., there was much induration around. The floor of the ulcer was formed by the pancreas. The appearance of the edges of the ulcer, however, did not suggest malignancy, and sections cut from two different places failed on microscopic examination to reveal any malignancy.

The curious features of this case were the age of the patient, the short history (six months) anorexia, loss of weight without much pain, the palpable mass with secondary anæmia, and the size of the ulcer, all in favour of a diagnosis of carcinoma. The raised acidity, though this occurs, it is said, in 20% of cases of carcinoma, was in favour of a non-malignant ulcer, as was the absence of glandular involvement; finally, microscopic examination was against malignancy. The specimen was shown.

Follow-up note.—The patient lost weight after the operation, but she was seen 18.5.50, in the Outpatient Department, and felt very well, and had started to gain weight.

Mr. Norman C. Tanner: I would like first of all to compliment Mr. McCurrich on this patient's excellent condition and her freedom from symptoms.

Resection of the pancreas together with the stomach is particularly satisfactory in those cases of carcinoma of the stomach where the lesion is of the locally invasive type in which distant glandular or peritoneal metastases tend to appear late. While the desirability of adding pancreatectomy is obvious in cases such as this, where the pancreas itself is invaded, it has also the advantage of removing the left suprapancreatic glands, which are the next in the line of invasion, and removal of the posterior wall of the lesser sac takes away the peritoneum in contact with and often invaded by posterior gastric wall carcinomas.

In my experience patients remain well and are able to work and eat normally after pancreatico-gastrectomy. The bowels may be a little loose at first, but after a few months they settle down to 2 to 3 slightly relaxed motions daily. I have not seen diabetes result from these partial pancreatic resections.

Splenectomy is of course a necessary adjunct to pancreatectomy and is often necessary or a matter of convenience after upper gastrectomy alone. Spreading thrombosis along the splenic vein to the portal vein with hepatic embolism has been reported after splenectomy, and in a series of 70 splenectomies reported by Quan and Castleman (1949), one died as a result of thrombosis involving the portal vein radicles, and four were found at post-mortem to have hepatic infarcts. This danger hardly seems sufficient to countermand splenectomy in carcinoma cases where it seems desirable.

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Mr. J. R. Griffith quoted a kindly examiner who showed him a case of resection of the stomach at a surgical examination, and remarked that whenever an operation for carcinoma of the stomach turned out successfully, the chances were 100 to 1 that the stomach was syphilitic. It need hardly be said that this happened many years ago.

Gastrocnemius Neurectomy.—H. J. MCCURRICH, M.S.

A man, aged 57, was referred for intermittent claudication. He experienced pain after walking 200 yards, worse in right leg.

In 1947 he had severe crush injury of his right arm. Rheumatic fever at age of 17, jaundice in 1917, dysentery and malaria in 1918. A hæmorrhage of the brain in 1920, and later coughed up blood three times.

The skin temperature curve showed a negligible rise after a spinal anæsthetic. Neurectomy of the right gastrocnemius.

On 9.2.50 the patient reported considerable improvement.

With the patient were shown his skin temperature tests before and after a spinal anæsthetic, a similar chart showing a good response in a patient with vaso-spasm, a diagram of the nerve supply of the gastrocnemius, and a nerve stimulator as used by Professor Seddon for establishing identity of nerve at operation.

Follow-up note.—The patient is back at work in a garage, and says he is free of cramps.

Mr. Rex Lawrie: Whether it is division of the motor or the sensory fibres that relieves the intermittent claudication, there is no doubt that ischæmia may affect one head only of the gastrocnemius or be localized to even smaller muscles. I recently saw intermittent claudication of the abductor hallucis cured by division of the nerve to that muscle.

[*May* 12, 1950]

Polycythæmia with Myelosclerosis.—M. S. R. HUTT, M.D., M.R.C.P. (for J. S. RICHARDSON, M.V.O., M.D.).

J. C., male, aged 67.

History.—Admitted to hospital 12.7.48 with a six months' history of increasing dyspnœa on exertion and tiredness. These symptoms had come on rapidly in January 1948. He was found to be anæmic and treated with iron and liver injections following which he made a rapid recovery. In June 1948 symptoms recurred and necessitated admission to hospital. Apart from clinical anæmia no other definite abnormalities were found on clinical examination.

Investigations.—R.B.C. 3,160,000; Hb 58%; C.I. 0·9; W.B.C. 20,300 (polys. 87·5%, lymphos. 4·5%, monos. 5%, eosinos. 2%, trans. neutrophils 0·5%, neutrophil myelocytes 0·5%).

Sternal marrow: Normoblastic hyperplasia.

Histamine test meal: Absence of free HCl in all specimens.

Occult blood: (3 specimens) 44 plus in each.

Barium meal, follow through and enema all normal.

In view of the rapid onset of symptoms on each occasion and the presence of occult blood in the stools the patient was considered to have bled from the gastro-intestinal tract. After transfusion and iron therapy he made a rapid recovery.

He remained well until January 1950 when he began to experience discomfort in the left hypochondrium and shortly afterwards became aware of a lump in this region.

Readmitted to hospital on 23.3.50.

The patient now appeared plethoric and was found to have an enlarged spleen reaching to the umbilicus.

Investigations.—27.3.50: R.B.C. 8,710,000; Hb 120%; W.B.C. 81,000 (polys. 42%, lymphos. 5%, monos. 1%, eosinos. 1%, basos. 1%, trans. neutrophils 32%, metamyelocytes 6%, neutrophil myelocytes 10%, myeloblasts 2%).

Sternal marrow: Normoblastic hyperplasia (obtained with some difficulty).

21.4.50: R.B.C. 6,640,000; Hb 108%; W.B.C. 55,000 (polys. 67%, lymphos. 4%, eosinos. 9%, trans. neutrophils 14%, metamyelocytes 6%).

X-ray of long bones: No abnormalities.

Marrow trephine: Marked myelofibrosis. No evidence of leukosis.

Comment.—The association of splenomegaly, a leukæmoid blood picture and a relatively normal marrow smear placed this patient into the group of conditions variously termed chronic non-leukæmic myelosis, agnogenic myeloid metaplasia or leuco-erythroblastosis. These patients usually present with anæmia though initial polycythæmic phases have been reported. Evidence of marrow fibrosis is usually found at autopsy and in this case was conclusively shown by bone-marrow biopsy. This clinical picture may also follow long-standing cases of polycythæmia vera and accounts for many of the cases in which leukæmoid blood pictures are associated with this condition. It is important to distinguish this group, as any attempt to reduce the abnormal blood picture by bone-marrow depressants, such as deep X-ray, will probably increase the speed with which anæmia develops.

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Malignant Exophthalmos with Ophthalmoplegia and Localized Myxœdema.—E. C. A. BOTT, M.B., B.Chir. (for J. S. RICHARDSON, M.V.O., M.D.).

Mr. J. I., aged 34.

History.—Protruding eyes for six months. No previous illnesses except conjunctivitis, 1947, which rapidly healed. Protruding eyes with watering, irritation and inability to close his eyes for six months, getting progressively worse. No thyrotoxic symptoms, but said to be getting fatter in the face and to have gained 1 stone in weight in the last year.

Examination.—Severe bilateral proptosis measured as rt. 3·3 c.m., lt. 3·1 cm., with blepharospasm and severe chemosis of the medial conjunctivæ of both eyes. No signs of hyperthyroidism. Bilateral tarsorrhaphy had been done elsewhere previous to admission, and both corneæ were now just covered when he closed his eyes. Weakness of both superior recti and inferior obliques.

Investigations.—X-ray skull normal. B.M.R. 11% (minus). Urine: 20·5 mg. of 17-ketosteroids in twenty-four hours.

Treatment.—Increasing doses of thyroid up to 5 grains t.d.s. and total dosage—276 grains in thirty-five days. Became toxic with degree of proptosis on 2.5.50, rt. 2·9 cm., lt. 3·1 cm. He has recently had stilbœstrol 5 mg. t.d.s.

Dr. E. Lipman Cohen: This man has an interesting lesion of the skin over his shin. It is raised and resembles pig's skin. It is circumscribed myxœdema. There are two varieties of this condition: (1) the Jadassohn-Dössekker variety, and (2) the kind which occurs in association with thyrotoxicosis. This is an example of the latter type. Most of those who have described it have given it a new name. I have called it "myxœdema circumscriptum thyrotoxicum" (Cohen, 1946). Klotz (1949) has objected to this name on the reasonable grounds that it is primarily a pituitary not a thyroid disorder. It is usually found when the thyrotoxicosis has some unusual feature. Dunhill (1937) found it in 3% of his cases. Curtis, Cawley and Johnwick (1949) have studied its occurrence in malignant exophthalmos. The lesion can be made to disappear with intracutaneous injections of hyaluronidase.

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Treatment of Congenital Adactyly by Pedo-Carpal Transference.—PATRICK CLARKSON, F.R.C.S.

Boy, aged 11, was born with complete absence of digits of the left hand and on that account is largely dependent on the help of others in such essential and simple functions as dressing and feeding (Fig. 1).

On the grounds that other methods of digital reconstruction offer very little hope of providing a gripping mechanism or any hand that could be made to look like a normal hand, the decision was made to transfer the five toes of the left foot to that hand. This stage has been completed. All the digits are present and viable. Toe extensors have been carried above the wrist and extensor function is present (Figs. 2, 3 and 4).



FIG. 1.—Pre-operative photograph. Note the intact first metacarpal of the left hand but the other digits are represented only by soft tissue buttons completely without function.



FIG. 2.—Showing the attachment of hand to foot after seven weeks. The digital vessels were divided at two and five weeks. Pedicles were in two stages.

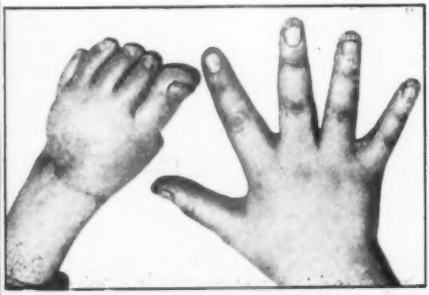


FIG. 3.—The result on detachment of the digits from the foot. Later surgery to establish a first cleft and provide digital movement by tendon grafts is to be undertaken before any function can be expected.



FIG. 4.—The foot. This has been repaired by tendon graft. He has no orthopædic disability.

Later stages will involve restoration of flexor function by free grafts and the establishment of a first cleft with the big toe transferred proximally and more into the palm to make a thumb. This repair has been planned to take place over a matter of two years in some twelve to fifteen operative stages. It is considered that the severe nature of the disability warrants such a prolonged treatment and that the best time for such operations is in early youth.

Pulmonary Fibrosis in a Paper Worker.—D. WEITZMAN, M.D.

This man, aged 63, presented two years ago with dyspnœa, productive cough and dyspepsia.

He has worked for forty years as operator of a machine for cutting book pages in a printing works. This is the only occupation he has ever followed. The atmosphere at the works was extremely dusty and analysis of a sample of the dust has shown it to contain 5·8% of silica.

Radiological examination shows a diffuse reticulation of all lung fields, with numerous "miliary" aggregations. There has been little change over the two years of observation. There is finger-clubbing, but no evidence of cor pulmonale. The sputum is mucoid, sometimes blood-streaked but never purulent, and repeated search has never shown any tubercle bacilli. No asbestos bodies have been demonstrated in sputum or after lung puncture.

The case appears to be one of pneumoconiosis and bronchiectasis due to siliceous paper dust.

Silica is used in paper processing in various ways. The common uses are in glazing paper (for which talc, a fibrous silicate, is used) and colour printing, in which china clay is used. Talc pneumoconiosis is well known among miners of this mineral; the lung reaction is similar to that seen in asbestosis and "asbestos bodies" are found in the lung.

The quantity of silica (5·8%) in the dust analysed in this case is not large, but the atmosphere at the works was extremely dusty. The inhalation, therefore, of large quantities of inert dust may have produced "blockage" of the lymphatics and hence rendered small quantities of silica more toxic than they otherwise would be.

It has also been suggested that the appearance in the X-ray may be due to the inhalation of printers' ink, which may be an iron-containing compound and radio-opaque. However, the case described has grave disability, and it is well established that "hæmatite lungs" with disability are, in fact, due to silico-siderosis.

Final proof will necessarily wait on post-mortem findings. It is premature to suggest that a new industrial hazard has appeared. Nevertheless, it cannot be ignored that the case shows an X-ray typical of pneumoconiosis and that a silica-containing dust has been inhaled. The case is presented in the hope of stimulating interest in the possible occurrence of this condition.

Dr. K. H. Lim: A patient of ours, now attending the Outpatient's Dept. at the Watford Peace Memorial Hospital, has worked for twenty years in a very dusty atmosphere as a paper warehouseman, but unlike Dr. Weitzman's case he is much younger, being only 39 years of age, has no symptoms and radiologically has no evidence of cor pulmonale.

He was first admitted about three months ago with a history very suggestive of bronchopneumonia and had typical clinical signs which cleared up on a course of sulphonamides. Radiologically he had fine mottling in all lung fields, which were coarsely mottled at the bases, but the latter disappeared about a fortnight later, i.e. prior to his discharge. One month after discharge, however, he still has fine reticulation in both lungs although he is completely symptom free.

As Dr. Weitzman has drawn attention to silicosis as an occupational hazard in paper works I shall certainly have the dust in this factory analysed for its silica content.

JOINT MEETING No. 1

Section of Endocrinology with Section of Orthopædics

Chairman—NORMAN CAPENER, F.R.C.S.
(President of the Section of Orthopædics)

[*Februcry* 22, 1950]

Fanconi-Type Resistant Rickets.—F. HARWCOD STEVENSON, M.D., M.R.C.P.

R. L., male.

Rickets diagnosed at 15 months.

When 2 years old, fitted with caliper which he wore for two years. At 4 years was in plaster for a short time.

March 1947: First seen at Royal National Orthopædic Hospital, Stanmore. Cod liver oil had been given for many years. X-rays showed active rickets.

Biochemical findings.—Serum inorganic phosphorus 2·3 mg.%, serum calcium 9·3 mg.%, serum alkaline phosphatase 162 units. Blood urea 37 mg.%. Urea clearance 63% of normal; urea concentration 2·75 and 3·20%. I.V.P. showed good concentration.

From May 1947 received 100,000 units vitamin D by mouth daily.

Glycosuria has been repeatedly noted. The sugar is definitely glucose. Blood sugar tolerance curve normal. Fæces show no excess of fat. CO_2 combining power of plasma 54·5 vols.%. Serum chlorides normal at 620 mg.%. Diastatic index 5 units per c.c. Total daily output of diastase 5,850 units.

August 1947: Osteotomy of lower end of femur on both sides as, by then, rickets radiologically well controlled.

Urine: Repeatedly excess excretion of amino-acids. Ammonia coefficient 4·9%. He appeared unable to acidify his urine either after violent exercise or following a dose of ammonium chloride. Frequent glycosuria and some polyuria.

September 1949: Serum calcium 10·1 mg.%, phosphorus 3·3 mg.%, alkaline phosphatase 30 units. Urine normal.

February 1950: Rickets radiologically controlled.

TABLE OF CLASSIFICATION OF RICKETS AND/OR OSTEOMALACIA
(*After* Dent; private communication)

Criteria: X-ray changes at the epiphyses and/or osteoporosis.
Low serum inorganic phosphorus.
Raised serum alkaline phosphatase.
Normal or slightly lowered serum calcium.

Types Known:

(1) Due to lack of vitamin D: Rickets. Hunger osteomalacia.
(2) Steatorrhœic rickets.
(3) Bile salt deficiency. ? Hepatic rickets. Experimental biliary fistula in dogs.
(4) Renal rickets.
(5) Rickets occurring with deficiency of renal tubular resorption but normal glomerular function. Tubular deficiency of varying degrees.

(*a* to *d*): *Often run in families.*
(*a*) Hyperphosphaturia only.
(*b*) Hyperphosphaturia and glycosuria.
(*c*) Excess phosphate, glucose and amino-acids in the urine: Fanconi syndrome.
(*d*) Excess phosphate, glucose and amino-acids in the urine with inability to acidify the urine, and, perhaps, deficient ammonia formation in the urine.
(*e*) *Does not run in families.*
Hyperphosphaturia with inability to acidify the urine and perhaps deficient ammonia formation without glycosuria or amino-aciduria: Nephrocalcinosis or renal acidosis or Butler-Albright syndrome.

Dr. C. E. Dent said the answer to the question of dosage was that one should seek chemical cure quite apart from radiological cure in a growing boy. The manner in which vitamin D acted was still very doubtful and controversial, but he had little doubt from his observations, and this was

supported by evidence in the literature, that vitamin D did also act on the renal tubules and improved the abnormally low reabsorption of phosphate. What was certain was that the plasma phosphate rose in response to vitamin D and fell again when the vitamin was no longer given.

He thought Dr. Stevenson's case was not acidotic and therefore did not need treatment by alkalis.

Cushing's Syndrome, Osteoporosis and Multiple Fractures.—A. A. G. LEWIS, M.D., M.R.C.P.

Male, aged 44.

1943: Increasing weight; headaches; polycythæmia and raised blood pressure.

June 1943: Called up for Army. August 1943: In military hospital with "infected ganglion" of foot. Glycosuria noted. Gained 26 lb. in two months. Invalided with diagnoses of diabetes mellitus, hypertension and polycythæmia.

1945–1949: Monthly venesections, at first one pint at a time, later two. Given 36 units soluble insulin daily.

During the last six years red cell count varied from 3,200,000 to 5,700,000, and the blood-pressure from 160/80 to 170/110.

Since 1943: Gained 2 stone. Thirst, polyuria, occipital headaches and dizzy attacks. Swelling of ankles. Fell down and broke his foot in December 1949. No pain in chest. Libido almost non-existent.

On examination (February 1950).—Round red face. Thin skin, with bruises and petechiæ, bruising on pinching. A few small striæ on shoulders. Obesity confined to trunk. Blood-pressure 175/105. Glycosuria.

Blood: R.B.C. 4,400,000; Hb 83%; W.B.C. 12,500; lymphos. 8%. Platelets, coagulation and bleeding times normal. Blood calcium 10·6 mg.%, phosphorus 3·0 mg.%, alkaline phosphatase 6·6 K.A. units, sodium 328 mg.%, potassium 20·5 mg.%.

Glucose tolerance test: 95 – 100 – 159 – 215 – 246 mg.%.

Glucose insulin tolerance test: 72 – 147 – 225 – 213 – 149 mg.%.

Urinary 17-ketosteroids 9 mg./twenty-four hours. Creatine 272 mg./twenty-four hours.

X-rays: Fractures of all but three of the ribs, several in more than one place. Some osteoporosis of entire skeleton, including skull.

The patient was admitted to the Middlesex Hospital under Professor A. Kekwick in December 1949, when the diagnosis was made and testosterone propionate therapy started.

22.2.50: Hæmoglobin 90%.



FIG. 1.—Intravenous pyelogram showing clearly the contrast between the density of the bones and the dye in the bladder.

In **Mr. L. R. Broster**'s experience, osteoporosis was more likely to be associated with Cushing's syndrome of the pituitary than with that of adrenal origin. He recalled a case seen during the war of a young girl with pituitary basophilism, more severe than was shown in the present case. She had a collapse of two vertebræ, and was treated in a plaster jacket. She was given an œstradiol implant, with Lugol's solution, a low calorie diet, and a fixed fluid intake, and in three months she was able to walk.

He had tried the same treatment with a testosterone implant in a man with Cushing's syndrome associated with an increased ketosteroid output, but it was not until unilateral adrenalectomy was performed that he showed any improvement. He had lost 2 stones in weight, but unfortunately was sent out of the ward for disciplinary reasons.

In reply to a question by Dr. Crooke, Mr. Broster said he thought that the ketosteroid test was a sound means of diagnosing between Cushing's syndrome of pituitary and adrenal origin.

Asked by Dr. Russell Fraser what the outlook was in the adrenal condition, Mr. Broster said that in hyperplasia there was improvement, and in tumour, apart from the appearance of secondaries, it showed marked improvement.

Dr. Lewis knew of certain cases in which one whole adrenal and a large part of the other adrenal were removed. He thought 2 of the cases survived, but it was a very radical operation.

Dr. A. W. Spence had had a patient with Cushing's syndrome who had slight hirsuties, amenorrhœa, osteoporosis of the vertebræ, hyperglycæmia, and a raised blood-pressure. The ketosteroid level was slightly raised. One adrenal was first removed, and it was found as a result of that that the blood sugar curve diminished considerably and the blood-pressure decreased, but not to normal. Subsequently the pituitary was irradiated, and the transformation was really remarkable. One could no longer recognize the individual. The hyperglycæmia disappeared completely, and the patient now had normal curves, regular menstruation returned and the blood-pressure fell to normal. After the removal of the adrenal the patient complained of severe pain in the spine, presumably due to the osteoporosis. Subsequently the pain disappeared after pituitary irradiation. The patient had been followed up in order to watch particularly the osteoporosis, but no change was observed. The irradiation of the pituitary was carried out during March 1948.

Dr. A. C. Crooke thought that X-ray therapy was generally disappointing. It should be tried in this case but if it failed radon seeds should be inserted into the sella turcica.

Dr. F. Parkes Weber asked when the polycythæmic or "bloated" appearance first developed. At all events he supposed it was there before treatment by venesections was started; but it did look as if these monthly venesections—at first one pint a month and later two pints—had produced extreme excess of blood in the body. Nothing tended to increase the total volume of blood in the body like periodical moderate bleeding. He did not know whether the volume of blood had been estimated in this particular patient or not.

Dr. Lewis said they were not responsible for the institution of this treatment, but actually the patient during this time had never shown polycythæmia at all. Whether he had retained fluid—and by such means diluted the haemoglobin—he could not say, but there was no evidence of this whatever. He did have œdema of the legs, possibly due to sodium and water retention, but there was no evidence of that now.

POSTSCRIPT (November 1950).—In April 1950 Miss Diana Beck inserted 2 radon seeds each of 0·5 millicurie into the pituitary, on the advice of Professor B. W. Windeyer. Unfortunately there has been little improvement, and radiotherapy is now being considered.

13.3.50: Dr. A. E. Kellie (Courtauld Institute of Biochemistry) estimated the urinary corticoid excretion by the phosphomolybdate method to be 4·43 mg./24 hours (normal range: 1·10–3·28 mg.).—A. A. G. L.

Dr. S. L. Simpson said that it was well established that plethora without polycythæmia was met with in Cushing's syndrome, and it was less rather than more usual to get polycythæmia together with plethora—whatever the cause of the plethora.

On the question which Mr. Broster had raised, it was undoubtedly true that in those cases of Cushing's syndrome due to an adrenal neoplasm, there was usually a considerable excess of 17-ketosteroids in the urine in contrast to those cases associated with hyperplasia, where the 17-ketosteroids might not be appreciably raised, although exceptions and diagnostic overlapping occurred. He could not agree that osteoporosis could serve as a differentiating point between adrenal hyperplasia and neoplasm. With the latter there was more likely to be a greater secretion of the corticosteroids (the S hormone of Albright) which produced so-called "osteoporosis" by breaking down protein, preventing nitrogen anabolism and the laying down of bone. There was also, however, a greater secretion of androgens (N hormone of Albright) which counteracted this and tended to produce nitrogen retention. Albright found that the giving of testosterone to patients with Cushing's syndrome led to the reversal of a negative nitrogen balance, a greater density of bone and diminution of bone pain and to the healing of pathological fractures.

On the whole, biochemists in this country had not found the highly elevated values for corticosteroids in the urine of patients with Cushing's syndrome as reported from some American clinics and this appeared to be true even when diabetes mellitus was present. Lineæ distensæ were not a prominent feature of this case and were absent from the abdomen. Red lineæ distensæ and other features of Cushing's syndrome had been produced in America by the cortisone therapy of rheumatoid arthritis (Personal communication, R. G. Sprague; R. G. Sprague *et al.* (1950) *Arch int. Med.*, **85**, 199; McNee, J. W. (1950) *Brit. med. J.* (i) 113). This was of considerable diagnostic importance and would permit the clinical diagnosis of adrenal hyperfunction (cortisone type) in conditions other than classical Cushing's syndrome if coloured lineæ distensæ were present, as distinct from white lineæ distensæ. Sprague had written the speaker to the effect that the waxing and waning of the red colour appeared to depend on the intensity of the injections.

The question of papillœdema associated with polycythæmia was interesting, and in a case of Cushing's syndrome in a male under Dr. Denis Williams, which he had kindly asked him (Dr. Simpson) to see, repeated venesections by his first assistant, Dr. B. G. Parsons-Smith, led to a subsidence and temporary disappearance of the papillœdema.

Vitamin-Resistant Rickets.—H. H. LANGSTON, F.R.C.S.

G. B., a male child of a district nurse, born 20.8.42, was brought to the Orthopædic Department of the Royal South Hants Hospital, Southampton, at the age of 3 years and 2 months, because of deformities of the legs and refusal to walk. He had been a healthy child at birth, and was breast fed for one year. He started to walk at the age of 12 months, but following a fall at approximately the age of 15 months, he had stopped walking, and had not walked since.

On examination he appeared to present the characteristic clinical and radiological appearances of florid rickets. His mother, being a district nurse, appeared to be well aware of the dietetic requirements of a child of this age, and the home conditions appeared to have been good and the diet fully adequate.

The child was admitted to the Lord Mayor Treloar Orthopædic Hospital, Alton, for further investigation and treatment.

Pathological findings.—Urine: No abnormality of concentration or content. Serum: Calcium 11·3 mg.%; phosphorus 2·1 mg.%; phosphatase: alkaline 30·6 units; acid 2·3 units. Blood urea 53 mg.%. There was no abnormality of the fat content of the fæces, either in the total, split or unsplit fat. The Wassermann reaction of mother and child was negative.

The boy was treated by vitamin D 200,000 I.U. daily for three months and 120,000 units daily for a further three months, and was also given calcium lactate and ascorbic acid. On this treatment the rickets appeared to heal; the serum calcium fell to 8·5 mg.%. After nine months' treatment the child was discharged on a maintenance dose of vitamin D, walking with knock-knee irons supplied on account of a residual genu valgum deformity. There was also some bowing remaining in the tibiæ.

On 27.10.47, five months later, the rickets appeared to have reactivated, and the epiphyses, which four months previously had presented a sharply defined healing appearance, had again become fluffy and irregular. He was readmitted to hospital, and as 300,000 I.U. of vitamin D by injection twice weekly, plus Adexolin minims 5 t.d.s., produced no improvement in four months, he was transferred to the care of Dr. Donald Hunter at the London Hospital.

8.5.48: The child, a boy of 5 years 9 months, weighed 2 st. 6 lb., height 3 ft. He had the marked clinical changes of rickets and was unwilling to walk or even stand. The X-rays again showed the typical appearances of florid rickets. The pathological investigations were as follows:

> Serum calcium 8·2 mg.%; inorganic phosphorus 4·3 mg.%; alkaline phosphatase 55 K.A. units. Urine: concentration normal, no albumin and no glycosuria. Sugar tolerance test within normal limits. There was no abnormality of the fat content of the stool, either in total fat, split or unsplit fat.

The child was treated with gradually increasing dosage of calciferol by mouth. Little clinical change was noticed during the first three months, but after three months in hospital on a dosage of 700,000 I.U. vitamin D daily, the rickets healed clinically and radiologically and the child was discharged home on 29.10.48.

Just over three months later, on 4.2.49, the child was again admitted to the Royal South Hants Hospital, Southampton, with a history of two weeks' vomiting followed by a fit. During the subsequent month the child's condition gradually deteriorated with fits of increasing frequency, and on 29.3.49, he became comatose and died.

POST-MORTEM REPORT

Emaciated very pale child with large head, domed forehead and parietal bosses. Skull bone thin; fontanelles closed. Great increase in C.S.F. over vault. C.S.F. clear.

Brain.—Dilatation of lateral third and fourth ventricles. There were areas of softening in both occipital lobes, extending to occipito-parietal region on right. Several sulci in the occipital and parietal lobes on both sides showed a layer of cortical calcification and in the right occipital lobe, just beneath the superior surface, there was a cavity 1 inch in diameter with calcification in its walls; it contained a few c.c. of cloudy fluid. The vessels in the base and surface of the brain did not appear to have abnormally thick walls.

Kidneys.—Cortices very indistinct and narrow. Capsules stripped with difficulty.

Ribs.—Beading at costochondral junctions.

C.S.F.—Urea 123 mg.%; calcium 8·4 mg.% (normal 4·5–6 mg.%).

MICROSCOPIC EXAMINATION OF THE CALCIUM DEPOSITS

Brain.—Largely in the grey matter of the cerebral convolutions, but also in the white, are areas of softening with calcium deposition. The nerve cells have disappeared and the areas are surrounded by phagocytes and newly formed blood vessels. There is a tendency for the calcium to be deposited away from the blood vessels, which appear as tubules surrounded by

healthy tissue running through masses of amorphous calcium deposits. No thrombosis of vessels is seen to account for the softening. The deposits appear to be extracellular.



FIG. 1.—Radiograph of arm on first admission to hospital, illustrating florid rachitic changes.



FIG. 2.—Radiograph of arm at the conclusion of the first period of in-patient treatment. Rickets radiologically healed.

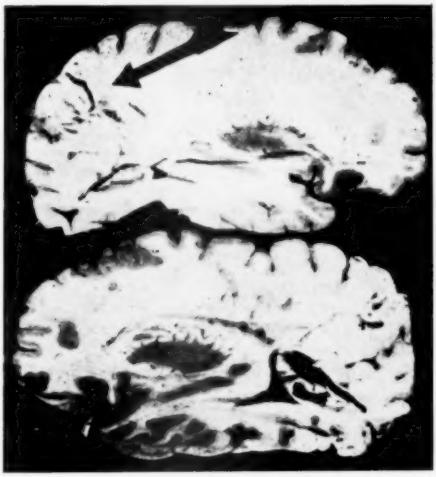


FIG. 5.—Post-mortem macroscopic brain sections. Note area of necrosis (arrow). Areas of cortical calcification in the cortex and frontal lobe are seen in both upper and lower sections.



FIG. 3.—Radiograph of wrist on second admission to hospital. Rickets reactivated.



FIG. 4.—Radiograph of wrist shortly before death. Rickets healed.

Kidney.—There is a general fibrosis. The convoluted tubules of the cortex are separated by well-formed fibrous tissue. Some are dilated and form microscopic cysts. The glomeruli are lobulated. Focal deposits of calcium salt are seen both inside and outside the collecting tubules. They appear as granules and masses which arise in the interstitial tissue between the tubules. The nuclei of the fibroblasts of the area become pyknotic and the cells necrose. There is frequently a feeble fibrous tissue capsule round the deposits. The deposits bulge under the epithelium of the tubules, and rupture into the tubules. In the cortex a similar process is seen. The deposit is both crystalline and amorphous. Many of the tubules show a heavy deposit in their lumen.

COMMENT

This appears to be a case of vitamin-resistant rickets in which the vitamin-D requirement progressively rose during the three years the child was under observation, until finally on the massive dosage of vitamin D necessary to keep the rickets under control, calcium deposits occurred in the brain and in the kidneys.

As far as I am aware, no case has previously been reported in which massive doses of vitamin D have led to the deposition of calcium in the brain and kidney with fatal termination, and the maximal safe dosage of vitamin D appears to require further consideration.

The ætiology of the condition is obscure and there appears to be no indication as to why this child required this high vitamin-D dosage to prevent the appearance of rachitic changes in the skeleton. Cœliac and renal rickets appear to have been excluded and there is no evidence that the child was an example of the Fanconi syndrome.

I am indebted to Dr. H. H. Gleave and to Dr. A. W. H. Foxell of the Pathological Department of the Royal South Hants Hospital, Southampton, for their reports on the post-mortem findings, and the microscopic sections, and to Dr. Donald Hunter for encouragement to report the case.

Dr. C. E. Dent asked whether the blood bicarbonate was determined, and on being told by Mr. Langston that it was not, said that it was therefore not possible to be quite certain what the diagnosis was. This made rather a difference whether the high dosage of vitamin D was likely to be toxic or not. Larger doses than the one mentioned in this case had sometimes been given without ill-effect.

Dr. Dent said that rarely when there were symptoms of vitamin D intoxication the blood level of calcium did not rise, yet by some mechanism the urinary secretion would be strongly increased. This could be detected in a rough-and-ready way by means of the Sulkowitch reagent.

Dr. Russell Fraser, on the question of a safe maximum dose of vitamin D, said that anybody having large doses of vitamin D should have the urine tested regularly for calcium with Sulkowitch solution, as a diabetic for sugar. The difference was gross when one got in the dangerous regions. That was the only safe device and it was very simple. But, of course, when one was dealing with a case primarily of renal disease, as this case, it would not always reveal the safe limit.

In the usual cases the morning sample of concentrated urine offered the best control basis; with renal cases, once the patient had been got under satisfactory control, knowing the blood level and the state of his bones, one did not allow him to deviate from that. It was an individual matter.

Calcium deposition in the brain was another interesting point. It had been observed in hypoparathyroidism where the mechanism, he imagined, was much the same. He did not know why it should occur.

Osteomalacia Secondary to Idiopathic Steatorrhœa.—P. I. HYWEL-DAVIES, F.R.C.S.

The patient, a woman aged 49, first attended the Orthopædic Department at Westminster Hospital on 7.12.49. She complained of recurrent backache of twenty years' duration.

History.—1929: Dyspepsia and hæmatemesis; investigated (negatively) at a hospital. The backache commenced after this period of hospitalization.

1933: Pain in the right loin and hæmaturia; backache became worse. Investigation at hospital was again negative. Her backache improved after this, and though the pain continued, it was never severe; but "weakness of the back" developed.

1936: Her back was manipulated at hospital with no improvement.

In 1941 she voluntarily took to her bed owing to the weakness in her back and legs, and remained in bed for eighteen months. During the first six months of this period her back "became bent" and her "chest deformed". She became ambulant when she felt stronger.

Her backache has continued since then. The curvature has changed neither for better nor worse. She sought advice at the Westminster Hospital because her pain was becoming more intense, and, in addition, she was becoming increasingly tired.

The backache is referred mainly to the lumbar region, is dull in nature, occasionally aggravated by movement, and relieved by rest.

Her appetite is fairly good, her weight steady, and her bowels regular.

Clinical examination.—Her general build is poor, and her stature shortened by the very marked rounded kyphosis (which is fixed). She has a gross pigeon-chested deformity, and a protuberant abdomen (Fig. 1).

Examination of her hip-joints reveals a marked limitation of abduction on both sides, and of rotatory movements; flexion is free.

X-rays (7.12.49) revealed generalized osteoporosis with multiple secondary pressure deformities in the pelvis, spine and bony thorax (Figs. 2 and 3).



FIG. 1.—Illustrates well the rounded kyphosis and the "pigeon-chest" deformity.



FIG. 2.

FIG. 2.—This illustrates the extreme porosis and "fish-tailing" of the vertebræ, which are so softened as to be quite unable to bear the normal weight—hence the kyphos.



FIG. 3.

FIG. 3.—Here the effect of weight-bearing on the softened bones is seen in the bilateral coxa vara and the marked trefoil pelvis.

Subsequent investigations (patient admitted 2.1.50).—From the preliminary clinical and radiological findings it appeared that the main differential diagnosis lay between hyperparathyroidism and some form of dietary or absorptive insufficiency.

Blood chemistry (5.1.50).—Plasma inorganic phosphates 3·8 mg.%; serum calcium 6·7 mg.%; serum alkaline phosphatase 25 K.A. units.

The low serum calcium excluded hyperparathyroidism. Renal hyperparathyroidism was excluded by normal findings for the urea clearance test and blood urea. There was no hypercalciuria.

Examination of fæces (7.1.50) showed a definite increase in the fat content: Total fat 36·2%, split fat 27·2%, unsplit fat 9·0% (=25% of total fat). Nothing abnormal was seen on microscopy.

These findings therefore suggested the diagnosis of osteomalacia secondary to idiopathic steatorrhœa.

It was decided to exclude pancreatic disease—the passage of a duodenal tube produced an adequate concentration of ferments, and trypsin was also found in the fæces (in a dilution of 1 : 20).

14.1.50: The blood chemistry and fæces estimations were repeated, with similar though less marked findings:

Blood chemistry.—Plasma inorganic phosphates 4·1 mg.%; serum calcium 7·7 mg.%; serum alkaline phosphatase 16 K.A. units.

Examination of fæces.—Total fat 28·5%, split fat 18·3%, unsplit fat 10·2% (=36% of total fat).

Although deemed unlikely, a gastrocolic fistula was excluded by a barium enema, and Fanconi's syndrome by a normal glucose tolerance test.

Conclusion.—The final conclusion was, therefore, that this was a case of osteomalacia secondary to idiopathic steatorrhœa, with inadequate absorption over many years.

I am indebted to Mr. H. E. Harding for permission to publish this interesting case.

Epi-metaphyseal Dysgenesis in Juvenile Hypothyroidism.—ALEX RUSSELL, O.B.E., M.R.C.P.

D. C., male, aged 11 years.

An atypical juvenile hypothyroid illustrating an unusual degree of dissociation of mental and skeletal effects. Normal mental and emotional development is linked with disproportionately severe failure of skeletal maturation and widespread epiphyseal dysgenesis. Attention is drawn for the first time, furthermore, to a widespread metaphyseal involvement akin to a dyschondroplasia.

The case was initially referred to Dr. Ursula Shelley on account of obesity and shortness of stature. She has kindly permitted this presentation.

Family history.—Mother: Antenatal fainting attacks. *Postnatal* persistence of anorexia, asthenia, apathy, with weight loss over eighteen months. Probably mild Simmonds' disease but hyperthyroidism not excluded. *Father:* Height 6 ft. No siblings. *Patient's grandmother.*—Menopausal myxœdema.

Personal history.—Although *milestones of development* were normal, with walking at approximately 1 year 2 months, he was disinclined to walk more than a few yards independently until over 5 years. *Speech* development apparently normal. Voice always nasal and husky. *Constipation* from late infancy until fifth year. *Increased thirst and polyuria* noticeable from age 2½ until 5 years. May have reflected a transient phase of diabetes insipidus as sequel to a hypothalamic encephalitic-like lesion. Smallness of stature and obesity increasingly apparent since fourth year. Pertussis at 3, right inguinal hernia at 5 and herniotomy at 7½ years.

Mental development.—Intelligence, mood and behaviour normal. Educational attainments average. Two independent observers (Miss M. McKinley and Mr. Sidney Crown) arrived at almost identical assessments: Raven's matrices: score 30. I.Q. 97. Stanford-Binet: Mental age 10 years 4 months., Form L. I.Q. 99. Rorschach test analysis: *Intelligence* average. Matter-of-fact, practical approach. *Interests:* Wide range. *Emotional:* Normal responsiveness.

Physical examination.—Weight 80 lb. (average range 57–71½ lb.). Height: 44¾ inches (average range 51·4–55 inches). Span 43¾ inches. Upper 24½ inches; lower 20¼ inches. Circumferences: Head 21¼ inches; chest 31½ inches; abdomen 32 inches. Dimensions principally reflect disproportionate retardation of leg growth. Possibly shortening and angulation at femoral neck, and compression effects at other joints of leg mainly contributory. Cheery, plethoric, moon-face. Bridge of nose broad, depressed. *Hair* coarse, close-knit curls. *Skin* dry, follicles prominent. *Hands and feet* dorsal padding. Palms square. Fingers and toes short and thick with blunt distal phalanges. Gross waddling gait. Lordosis. *Teeth:* All deciduous. *Maximal fat deposition:* Supraclavicular and dorsal cervical pads. Mammary region. Lower abdomen. *Thyroid* not palpable. C.V.S. Pulse-rate 90/minute. Blood-pressure 125–135/75–80.

RADIOLOGICAL INVESTIGATIONS

Carpus.—3 centres of ossification only.

Other epiphyses.—In all, varying degree of stippling, porosity, fragmentation either throughout structure or only in periphery, characterizing hypothyroid dysgenesis. Distribution of centres and changes therein support other features suggesting main skeletal impact of hypothyroidism in his third year.

Femoral heads.—Gross changes in femoral capital epiphyses. Left side shows only a lateral segment, comprising a small distorted fragmented zone. Right shows only a few scattered osseous nuclei.

Metaphyseal changes.—Structural disturbance not confined to epiphyses as customarily accepted in hypothyroid dysgenesis. Metaphyses grossly involved especially femoral neck and distal tibia (Figs. 1 and 2) both subjected to the greatest pressure moulding effects. In both, areas of condensation enclose, or are interspersed with, rarefied zones (circular or linear) opening towards epiphyseal line. Similar changes in acetabulæ. Lateral half of epiphyseal cartilage lines at both knees and ankles obscured by apparent bridge of irregularly calcified material. Impression may be due to abnormal obliquity of epiphyses upon diaphyses, not uncommon in hypothyroidism. Possibly due to actual weakening or destruction of cartilage of epiphyseal line. May account for slipped epiphyses seen in hypothyroidism (Miller and Benjamin, 1938). Condensation of metaphyseal line well illustrated in phalanges (Fig. 3).

Vertebral "infantilism" present with persistence of bobbin-like outline of body.

Thorax.—Triangular cast with sharply narrowed upper thorax attributable to failure of longitudinal growth of ribs.

Metacarpals and metatarsals each show an accessory centre, distally placed in first, proximally in remainder. Not uncommon in advanced hypothyroidism (Holt and Hodges, 1945), and seen also in various chondrodystrophies.

Laboratory Investigations

Blood: Hb 84–92%; R.B.C. 4,400,000–5,400,000. Wassermann reaction and Kahn test negative.

Serum cholesterol	Range 340–450 mg.%
Alkaline phosphatase (K.A.)	„ 5·9–7·7 units
Serum calcium	„ 11–12 mg.%
Plasma inorganic phosphates	„ 2·5–4·0 mg.%
Serum protein: Total	„ 7·48–7·97%
Albumin	„ 5·03–5·68%
Globulin	„ 2·29–2·45%
Non-protein nitrogen	24–43 mg.%
CO_2 combining power	53·8 vols.%
Sodium	315 mg.%
Chlorides	620 mg.%
Potassium	20 mg.%

Urine: Creatine coefficient = 0·18 to 0·30 (normal = approx. 2·7); 17-ketosteroids: 2·1–2·7 mg./twenty-four hours.

Carbohydrate metabolism.—Dextrose tolerance test reflected relatively impaired tolerance:

40-gramme dose: 88 mg.% rise in thirty minutes
50-gramme dose: 112 mg.% rise in sixty minutes
Still 40 mg.% above fasting level in two and a half hours

Insulin tolerance test: Range of fall in three tests (3·8 units i.v.) was 28–40% of the fasting level. Return to normal: sixty minutes.

Adrenaline tolerance test: Flat curve with minimal rise of 9 mg.% in one hour.

Galactose tolerance test: Low hypothyroid curve with only 14 mg.% rise in thirty minutes. Fasting level in sixty minutes.

Electrocardiogram.—Low voltage T waves only.

B.M.R.—Three readings: −7%, −13%, −22%.

Thyrotrophic hormone test incorporating assessment of radioactive iodine uptake and urinary excretion, kindly performed by Dr. Russell Fraser. No significant response.

Iodine excretion, measured as percentage of oral dose

	Dosage	Hours from time of oral dose 0–8	8–12	12–24	24–48	Total
Before Ambinon administration (11.6.49)	10μc.+10γKI	32·8	8·3	9·7	8·0	58·8%
During Ambinon administration (25.6.49)	10μc.+10γKI	43·0	11·8	10·1	3·9	68·8%

Iodine uptake.—Fifty-six hours after tracer dose, counts suggested 5% or less of dose present in neck.

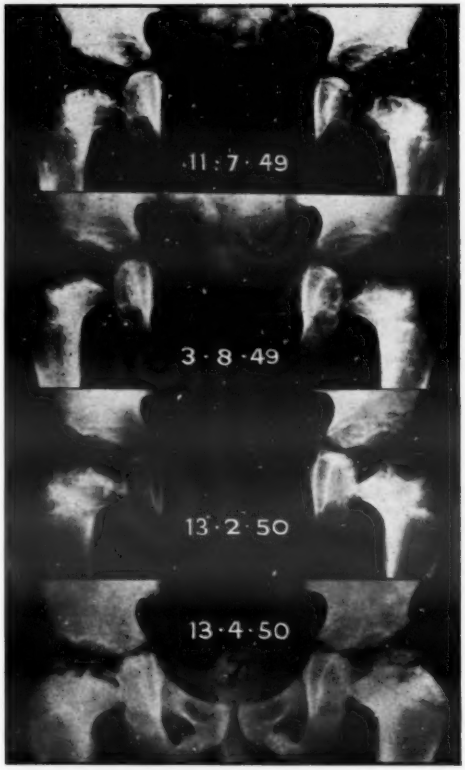
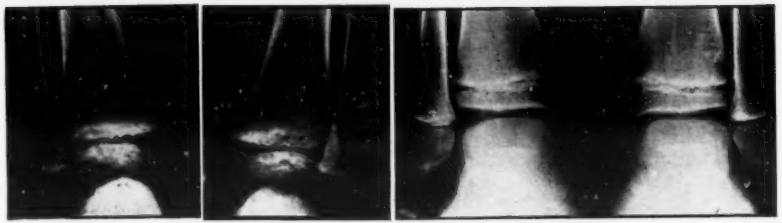


FIG. 1.—Femoral head and neck: Transition towards normal shape, density and homogeneity on left side during thyroid therapy.



Pre-therapy. FIG. 2.—Ankles. Post-therapy (7 months later).

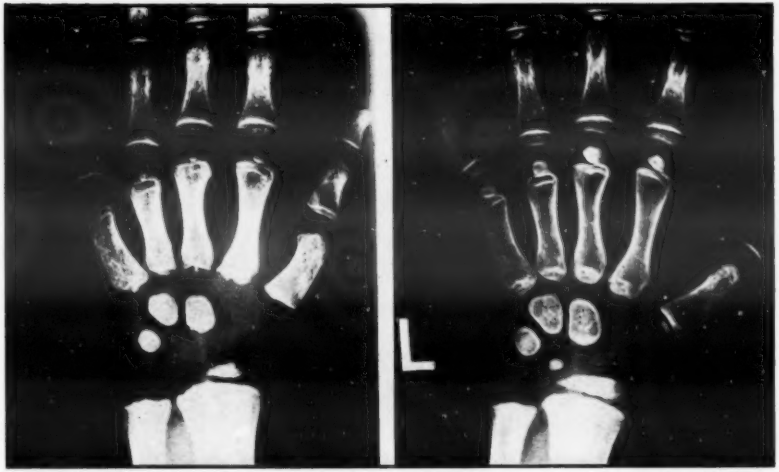


FIG. 3.—Hands. Pre-therapy: 3 carpal centres. Accessory centres to metacarpi. Metaphyseal lines of condensation typical of hypothyroidism. Post-therapy (2½ months): Two more carpal centres. Fusion of accessory centres. Abnormal shadows of expansion of metacarpal epiphyses superimposed upon original centres.

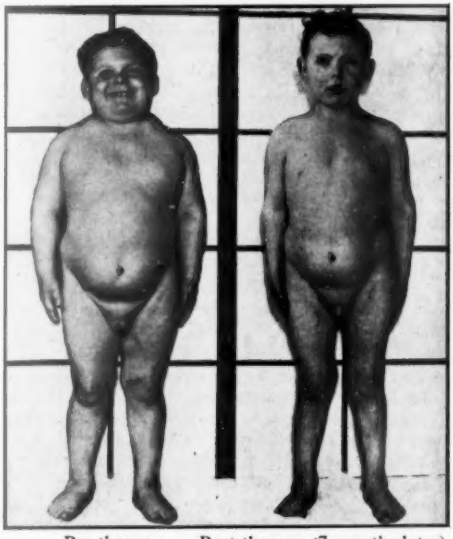
Test revealed neither the increased avidity of thyroid for I^{131} nor decreased excretion rate expected as a positive response to thyrotrophic hormone, if defect is primarily pituitary (Reiss, 1949). Since a control treated synchronously showed equivocal response, the potency of the preparation used was in doubt, but it was not possible to repeat the test.

Adrenotrophic test.—84% depression of eosinophil count four hours after adrenaline injection, implying adequacy of pituitary/adrenal reserve.

RESPONSE TO THYROID

13.7.49: *Initiation of thyroid therapy* on basis of diagnosis of primary hypothyroidism. Dosage: Slow gradation from ¼ grain (32 mg.) to 3 grains (194 mg.) daily. Return to 2½ grains (162 mg.) daily for past three months.

Biochemical response.—Serum cholesterol: Fall of 228 mg.% in six weeks (from 353 to 125 mg.%). Alkaline phosphatase: Peak figures of 16–19 units coincided with trough of serum cholesterol decline. Probably reflected increased osteoblastic activity synchronizing with progress in epi-metaphyseal picture. Galactose tolerance curve: Striking swing from typically low pre-therapy curve to one showing strongly hyperthyroid pattern (160 mg.% rise in thirty minutes).



Pre-therapy. Post-therapy (7 months later).

FIG. 4.

Radiological response.—Femoral heads (where changes always of greatest severity and persistence): Left: First ossification in medial segment after two months. The lateral segment gradually assumed rounded cap-like outline within seven months (Fig. 1). Right: Progress slow. Increased calcification only. Progressively improved homogeneity and density of femoral neck.

Knees and ankles.—Rapid increase in size, improvement in homogeneity, coherence of outline of epiphyses. Improved homogeneity and density of metaphyses (Fig. 2).

Hands and feet.—Rapid appearance of fresh carpal and tarsal ossification centres and fusion of accessory centres (Fig. 3).

Clinical response.—Mental: Reassessment 21.2.50 (Mr. Sidney Crown and Miss S. M. Cox): Trend towards imaginative, apprehensive, anxious hyperthyroid. Although slight increase in small detail responses and tendency to more critical approach, intelligence level on the whole decreased since initial testing with a fall in I.Q. by 12–17 points, viz.:

Raven's matrices: score 20. I.Q. 86. (Pre-therapy 30 and I.Q. 97.)

Stanford-Binet: Form M. Mental age: 9 years 8 months. I.Q. 87. (Pre-therapy results: I.Q. Form L. 99.)

Rorschach test, &c.: Confusion and emotional impulsiveness not shown previously.

Physical: Transformation conveyed by Fig 4. Rapid progress in growth: increment of 4 inches in seven months. Dispersal of fat pads within three months. Total weight lost in

first six months 20 lb.; none subsequently. Within three months the skin became smooth; the hair soft and lustrous; the voice soft and without nasal twang. Bridge of nose assumed normal shape. Waddling gait disappeared within three months, although femoral heads showed no appreciable calcification. Improvement in power and tone of muscles of pelvic girdle probably principal factor.

Discussion

In view of anomalous features and striking dissociation of mental and skeletal changes, it is worth while to assess, as precisely as possible, the degree of impairment of thyroid function, and the contributory role played by the pituitary in this respect.

Only partial hypothyroidism was demonstrable. The absence of an associated pituitary defect was indicated by:

(*a*) Insulin tolerance tests, in which consistently decreased sensitivity and moderate hypoglycæmic responsiveness as described in primary hypothyroids (Fraser *et al.*, 1941) contrasting with the hypersensitivity and unresponsiveness in pituitary hypothyroidism.

(*b*) Normal 17-ketosteroid excretion and normal gonads.

(*c*) Absence of significant response to thyrotrophic test.

(*d*) Normal response to adrenotrophic test.

The mild hypertension, plethoric moon-face, a superficially buffalo-like concentration of fat around short neck and shoulders and upper thorax, and the impaired glucose tolerance and insulin sensitivity could be combined to give a clinical impression of a Cushing's syndrome variant. The gross osseous changes, however, specifically characterize hypothyroidism and proved the principal diagnostic criterion, although the discrete character of the fat pads and other classical features of hypothyroidism gave strong support. To what extent a degree of chronic pituitary hyperactivity, initially compensatory to primary thyroid lack, and subsequently including adrenocorticotrophin overproduction, could play a part in inducing features recalling Cushing's syndrome, is an interesting speculation. Excess adrenotrophic stimulation could have contributed to the disproportionately severe skeletal changes since retardation of chondro-osteogenesis has been demonstrated experimentally in response to excess A.C.T.H. administration (Becks *et al.*, 1944).

The metaphyseal changes resemble those seen in dyschondroplasia where metaphyseal defects are dominant. Scanty studies in hypothyroid bone pathology revealing persistence of islets of cartilage together with liquefactive and fibrotic changes in cartilage (Looser, 1929) suggest more than a superficial radiological likeness.

The deterioration of mental function recorded is disappointing and is presumably attributable to confusion, &c., induced by excessive stimulation of relatively unaffected cerebration by a thyroid dosage high enough to promote skeletal progress. This explanation is equally applicable to treated hypothyroids in whom improved psychological performance results from controlled reduction of thyroid dosage, rather than its increase (Wilkins, 1938). Stabilization on lower thyroid dosage was unavoidable in this case to permit undisturbed mental function and progress. Supplementary use of growth hormone is planned principally to achieve optimal skeletal stimulus in spite of the reduction of thyroid dosage thus indicated.

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The following cases were also shown:

Osteomalacia, Milkman's Syndrome and Renal Insufficiency.—F. T. G. Prunty, F.R.C.P., and R. R. McSwiney, M.B.

Osteomalacia—R. I. S. Bayliss, M.R.C.P.

Section of Anæsthetics

President—GEOFFREY ORGANE, M.D., F.F.A. R.C.S.

[*May* 5, 1950]

Differential Spinal Block

With Particular Reference to Hypertensive Patients

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PROBABLY a discussion of Differential Spinal Block should begin with a definition. The term "differential" applied to a regional or spinal block means only that the method is selective of certain groups of fibres. It has been demonstrated that such a block by the subarachnoid route is possible and some of the groups of fibres affected by it have been identified. It is not suggested that this or any other technique of regional blocking is capable of making a differential diagnosis.

For many years surgeons and anæsthesiologists have been aware that it is possible to produce subarachnoid block of sensory fibres accompanied by little or no motor paralysis. It was demonstrated by Gasser and Erlanger [1] using cocaine and by Heinbecker, Bishop, and O'Leary [2], in 1934, using procaine that when a solution of either of these drugs is deposited around a mixed nerve, blocking of all fibres does not occur simultaneously. On the contrary, the small, unmyelinated fibres are blocked first; and other fibres are affected in sequence according to their size and myelinization. Essentially the same sequence supervenes when procaine is introduced into the subarachnoid space. The effect upon nerve fibres is apparent in the following order: autonomic vasoconstrictor fibres, temperature, pain, motor, joint sense, pressure sense and touch. It has been suggested that the reason for this sequence is that the small fibres are susceptible to a lower concentration of the local anæsthetic drug than the larger ones. The effort to produce a differential spinal block was undertaken upon the premise that this is the correct explanation and that therefore it should be possible to introduce into the subarachnoid space such a concentration of procaine as to paralyse the small and spare the larger fibres.

The method and equipment for the maintenance of subarachnoid block by continuous infusion were introduced by Arrowood and Foldes in 1944 [3, 4]. Differential spinal block described by Sarnoff and Arrowood in 1946 [5] is produced by the application of this method, using procaine hydrochloride in a concentration of 0·2% in 0·85% solution of sodium chloride. For induction 10–20 c.c. of the dilute procaine solution is rapidly introduced during a period of three to four minutes. Infusion is then continued at a rate of 1–1·5 c.c./minute.

The fibres affected by subarachnoid block with 0·2% procaine are the C fibres. They are small, and have little or no myelin sheath. Table I lists the fibres which are paralysed and those which are spared by differential spinal block.

TABLE I

The fibres which are blocked, and those which are spared when procaine hydrochloride in 0·2% solution is infused into the subarachnoid space.

Fibres blocked	*Fibres spared*
Vasomotor	Touch
Sudomotor	Position sense
Visceromotor (Thoracolumbar and sacral outflows)	Vibration sense
Pin-prick sensation	Pain, types other than pin-prick
Stretch afferents	Somatic motor

Effect Upon Cardiovascular System

The effects of differential spinal block upon the cardiovascular system which have previously been described by Sarnoff and Arrowood, 1946–48 [6–9] may be summarized as follows:

When 0·2% solution of procaine is infused into the subarachnoid space of a normotensive patient, a fall in blood pressure occurs when the differential block ascends to such a level that it affects the sympathetic fibres of the thoracolumbar outflow. The extent of block necessary to cause this fall in blood pressure varies from one patient to another. Sometimes the decline in blood pressure begins at about the same time as the rise in skin temperature of the lower extremity. In other patients there is no appreciable change in the blood pressure until the differential block extends to the upper thoracic segments. There is often a decrease in the pulse rate concurrent with the beginning of the rise in skin temperature of the upper extremity. The level at which the appreciation of pin-prick is impaired does not always correspond with the level of effect upon the vasoconstrictor fibres. For example, one patient whose chart showed a marked fall in blood pressure beginning simultaneously with the rise in temperature of the lower extremity never had any impairment of sensation except on a very small area on the medial aspect of each thigh, while another whose blood pressure did not change significantly at all had a level of analgesia to pin-prick to the level of the fourth rib anteriorly.

If differential block is extended to such a level that there is either a definite bradycardia or a rise in skin temperature of the upper extremity, the blood pressure will fall. If this fails to occur with the patient in the supine position with the table level, it becomes immediately apparent if the head of the table is elevated 10 or 15 degrees. In some individuals a marked fall in blood pressure occurs in the absence of either bradycardia or rise in skin temperature of the upper extremity.

One of the explanations which has been offered for the fall in blood pressure during spinal anæsthesia is that paralysis of skeletal muscle results in decreased venous pressure and thus stroke volume and cardiac output are decreased. In an effort to obtain additional information as to the importance of this factor in the hypotension incident to spinal anæsthesia, we administered full spinal block sufficient to cause complete motor paralysis of the lower extremities and of the abdominal muscles to 6 patients at the end of the administration of differential spinal block. In no case was there a significant fall in blood pressure following muscular paralysis beyond that which had already occurred following the differential block of the autonomic fibres. These results fail to support the idea that paralysis of skeletal muscles is a major factor in causing the hypotension incident to spinal anæsthesia, but add likelihood to the explanation that it is caused chiefly by the decrease in peripheral resistance which results from interruption of transmission of autonomic vasomotor impulses.

Differential spinal block has been administered to 18 hypertensive patients in the course of their evaluation with a view to surgery. They were subsequently followed for a period of two to three years.

In general, when differential block is administered to hypertensive patients the same sequence of events tends to occur as in normal individuals. However, the fall in blood pressure often is steep and profound. We were interested in observing the effect of differential spinal block upon the ability to respond to cold as well as its effect upon the blood pressure and the pulse rate. The cold pressor test consists in having the patient place one hand in ice water while blood pressure and pulse readings are charted at half-minute intervals for two minutes.

Various types of response are seen when we examine the charts summarizing the events during differential block of different hypertensive patients. The responses of a woman aged 34 are shown in Fig. 1. Reading from above downward are shown: blood-pressure readings, pulse rate, and skin temperature recorded in degrees Fahrenheit. The capital letters with numbers represent the level to which there was impairment of appreciation of pin-prick. The black blocks indicate cold pressor tests. The time of lumbar puncture is marked by the arrow. Following placement of the needle, there was a period of rest in order to stabilize the blood pressure and skin temperature levels. The space between the two vertical lines represents the duration of the subarachnoid infusion of dilute procaine solution. In this patient there was a marked rapid fall in blood pressure beginning about the time of the rise in skin temperature of the lower extemity. Although the infusion was continued until there was impairment of appreciation of pin-prick to the level of the angle of the jaw, there was no rise in skin temperature of the hand, nor was there a slowing of the pulse rate. The ability to respond to cold by a rise in pulse rate and blood pressure was markedly impaired by the block. The rise in blood pressure just before the second cold pressor test and just after the infusion was stopped occurred during bouts of retching, and was probably the result of increased intra-abdominal pressure.

Fig. 2 shows the responses to posture and cold in the same patient before operation, and twenty-four months post-operatively. These charts are prepared as follows: after a period of rest, blood pressure and pulse readings are recorded at one-minute intervals for five minutes with the patient supine, then sitting, and then standing. The second section of the chart shows the cold pressor reaction with the patient supine, then standing. It is evident

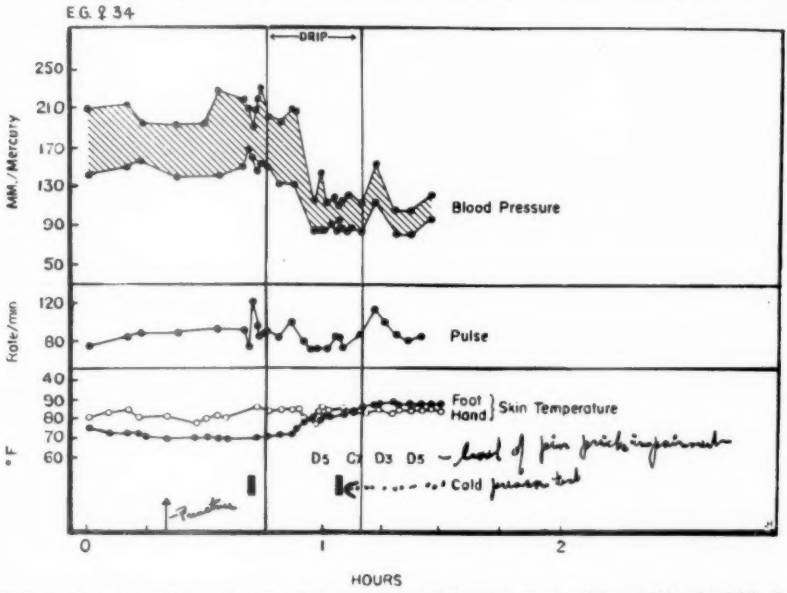


FIG. 1. Pre-operative response of hypertensive patient E. G. to differential spinal block.

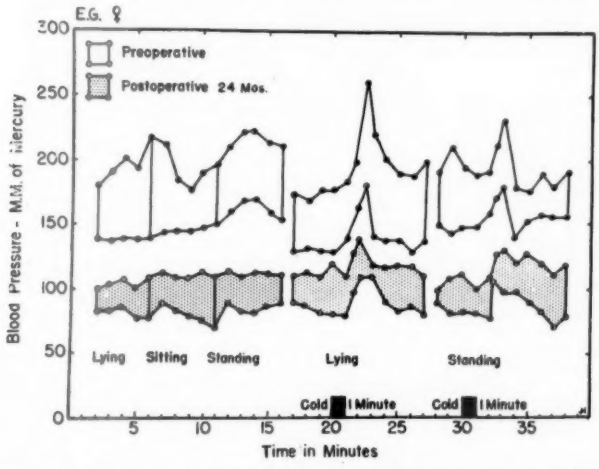


FIG. 2. Response to posture and cold before operation and 24 months post-operatively of patient E. G.

that the blood-pressure levels and the pulse pressure before and twenty-four months after operation are similar to those observed immediately before and during differential block.

Fig. 3 demonstrates the response of a man 34 years of age. In this instance decline in blood pressure was much more gradual. The response to cold was considerably diminished. The infusion was continued until a rise in skin temperature of the hand occurred.

The cold and posture responses of this patient before operation and thirteen months post-operatively appear in Fig. 4. It will be observed that the blood-pressure levels before and after operation are within the same range as those which were seen just before and in the course of the differential spinal block.

A different type of response which occurred in a 39-year-old woman with severe, long-standing hypertension is shown in Fig. 5. It will be noted that although the block was ex-

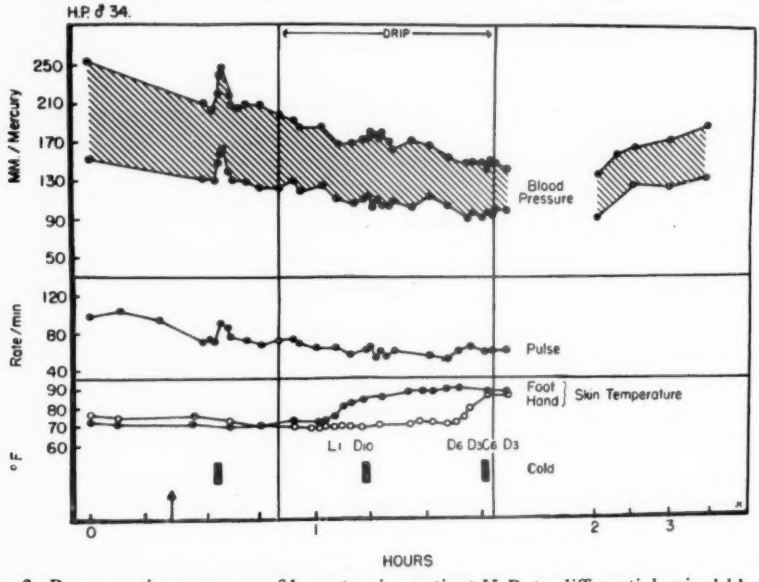


FIG. 3. Pre-operative response of hypertensive patient H. P. to differential spinal block.

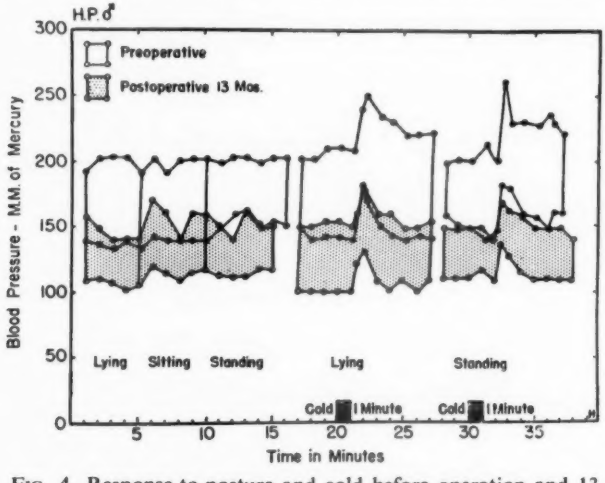


FIG. 4. Response to posture and cold before operation and 13 months post-operatively of patient H. P.

tended until there was a rise in skin temperature of the upper extremity and an appreciable slowing of the pulse, there was very little change in the blood-pressure level. The response to cold, however, was much diminished. It is of some interest to notice the decrease in skin temperature of the upper extremity coincident with the rise in the lower extremity until the block ascended high enough to affect the upper thoracic segments and resulted in a rise in the

temperature of the hand and a fall in the pulse rate. Splanchnicectomy was not performed in this patient because the pre-operative studies revealed that she was not a suitable candidate.

Fig. 6 is a chart of the events during differential spinal block of a 52-year-old woman with very severe hypertension. This patient had marked cardiac hypertrophy and a severe tachy-

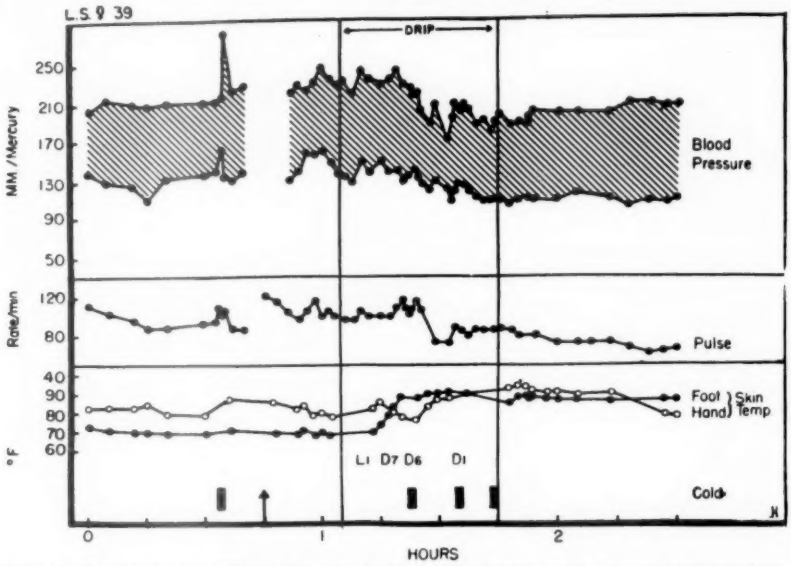


FIG. 5. Response to differential spinal block of patient with severe hypertension of long duration.

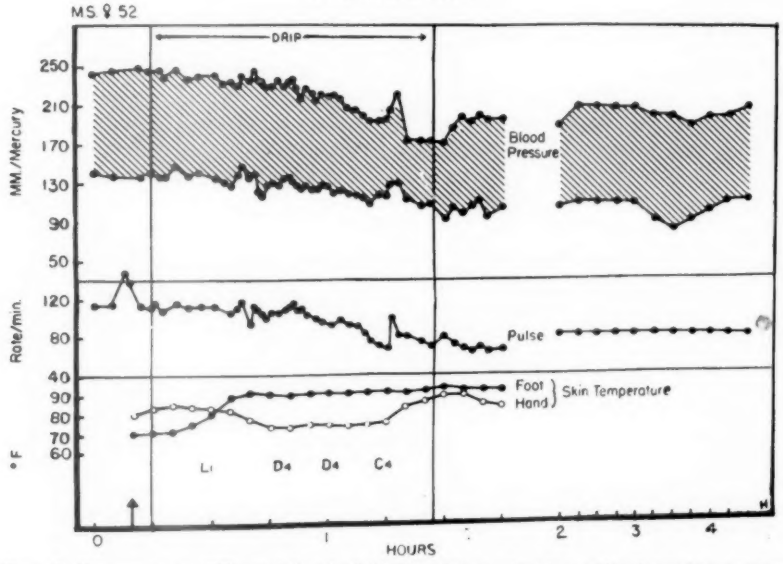


FIG. 6. Response to differential spinal block of hypertensive patient having severe cardiac involvement.

cardia with a right bundle-branch block. A gradual decline in the blood pressure began contemporaneously with the rise in skin temperature of the lower extremity and reached its lowest level after the block was extended to involve the upper thoracic segments as indicated

by the rise in skin temperature of the hand. There was marked slowing of the pulse rate. The borrowing and lending phenomenon with decline in skin temperature of the upper extremity coincidental with rise in the lower extremity is even better illustrated in this case than in the preceding one. An interesting phenomenon occurred in this patient. When the effect of the differential spinal ascended to the level of the upper thoracic segments, the bundle-branch block disappeared but it reappeared three days later. Splanchnicectomy by the thoracic route with denervation from D_2–D_{12} inclusive was followed by disappearance of the heart block for several months.

The response to differential spinal block in a 41-year-old man who, five years previously, had had a lumbodorsal splanchnicectomy is shown in Fig. 7. At the time of this study the

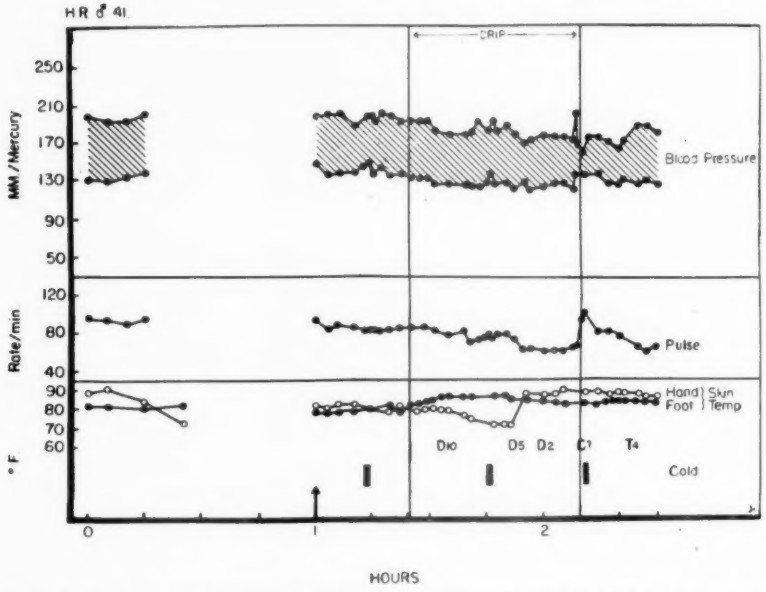


FIG. 7. Response to differential block of hypertensive patient who had bilateral lumbodorsal splanchnicectomy five years previously.

advisability of extending sympathetic denervation to include the upper thoracic segments was being considered. It will be noted that even in a cold room there was no change in the skin temperature of the feet since they had already been denervated at the previous operation. As the block ascended there was a very slight rise in temperature of the lower extremity with an accompanying fall in the temperature of the upper extremity until the block ascended to the upper segments when rise in the skin temperature of the hand followed. Even though the differential block in this case was extended to such a level that it caused rise in skin temperature of the hand and marked drooping of the eyelids, and constriction of the pupils bilaterally was observed, there was very little change in the blood-pressure levels.

DISCUSSION

Observations on the effect of differential spinal block upon blood-pressure levels and heart-rate are considered significant from two standpoints:

(1) Their bearing upon the choice of spinal anæsthesia in certain types of patients.

(2) The validity of the use of spinal anæsthesia or other techniques of regional blocking for the purpose of selecting hypertensive patients for surgery of the autonomic nervous system.

Spinal Anæsthesia in Hypertensive Patients

When spinal anæsthesia is administered to an individual to produce complete block of a given area, it may be observed in testing the level of analgesia from below upward that there is a point at which a change in appreciation of sensation occurs. Below this level the patient does not perceive any stimulus, either touch, or sensation of pressure, or prick. Above this line there is some sensation. He perceives touch, but does not perceive the sensation of

sharpness of a pin. Some segments higher there is another line above which perception of all sensations is unimpaired. The area between these two levels is partially or differentially blocked. The concentration of agent in the spinal fluid which produces this block is usually adequate to produce, also, a block of the vasoconstrictor fibres to that level. When spinal anæsthesia sufficient to perform major surgery in the upper abdomen is induced and maintained for a considerable period, the area of differential block may extend to a level which amounts to complete sympathetic decentralization. Evidence of this fact may often be observed in the warm, dry skin of the hand and arm and in the dilatation of the veins of the upper extremity of the patient under high spinal block. Sometimes the entire body is very dry except for a few beads of sweat on the face, around the nose and on the forehead. Toward the end of the operation, the block begins to recede and one may observe the beginning of sweating as beads of sweat appear on the neck and gradually at lower levels on the upper part of the trunk. It does not necessarily follow that such a complete sympathetic differential block occurs in all patients who undergo high spinal anæsthesia, but it probably occurs in the majority. In patients with normal cardiovascular systems it is possible by the use of the synthetic vasopressor amines to maintain the blood pressure and to keep the patient in good condition under such circumstances. But it is recognized that the results of spinal anæsthesia in hypertensive patients, particularly those who have myocardial or hypertensive heart disease, occasionally are disastrous. Spinal anæsthesia rigidly confined to the lumbar distribution for surgery of the lower extremity or perineum may be the anæsthesia of choice in hypertensive patients. In such a situation the vasoconstrictor supply to a large part of the vascular bed remains intact and is capable of increased compensatory activity. This is demonstrated by the fall in temperature of the upper extremity coincident with the rise in the lower. However, when the planned extent of the block includes the thoracic segments, the effect upon the autonomic fibres of the thoracolumbar outflow paralyses the effector mechanism of homeostasis, as is demonstrated by the inability of the patients to respond to the stimulus of cold. Sometimes hypertensive patients who have an acute paralysis of the thoracolumbar outflow, particularly if considerable blood loss has occurred, become refractory to the effect of the vasopressor amines, and a long period of severe hypotension results. It occasionally happens following long operations under spinal anæsthesia, or following splanchnicectomy, that it is impossible to restore the blood pressure to satisfactory levels in spite of adequate blood and fluid replacement, and the patient succumbs to shock. It appears, therefore, that except when it is of limited segmental distribution, spinal anæsthesia is relatively contra-indicated in patients with essential hypertension.

The Selection of Hypertensive Patients for Sympathectomy

Because the beneficial results of sympathectomy in hypertension are the result of the interruption of transmission of impulses over the autonomic nervous system, it has been suggested that some type of regional block might be of value in selecting patients suitable for surgery, by indicating the fall in blood pressure to be expected and the extent of sympathectomy to be undertaken. Various methods suggested have included paravertebral block of the sympathetic ganglia, spinal anæsthesia, continuous caudal block extending into the lumbar and thoracic segments, and differential spinal block.

The selection of hypertensive patients for surgery presents a complex problem. It has been pointed out by Smithwick in 1948, 1949 [10, 11] that three factors—nervous, humoral, and vascular disease—appear to affect the peripheral resistance in hypertensive patients. Theoretically if all co-exist in equal importance, the removal of any one would not affect the blood-pressure levels; but if one is dominant, its removal should result in a lowering of blood pressure to the level at which the others are operating. Considerable difference of opinion exists as to which of these factors initiates the disorder. The objective of surgery is to delay the progress of cardiovascular disease not only by lowering the blood-pressure levels but by reducing the reflex variations in the blood pressure which occur as a result of stress. There is some reason to believe that the latter effect is of equal and possibly of greater importance. A review of the results of surgery in patients over a five-to-ten-year period has shown that, judged by the relief of symptoms and improvements in the cardiovascular status, many individuals may be improved for years even though the effect of operation upon blood-pressure levels is significant but temporary or the basal levels are never significantly lowered.

The hypotension which results from any regional block is the acute effect of a chemically induced denervation or decentralization. Wilkins, 1950 [12], draws attention to the fact that the long-term treatment of chronic disease is a different matter from the short-term treatment, and that in essential hypertension the patient is unusually susceptible to the immediate effects of hypotensive drugs and procedures. By following patients carefully over a long period of time post-operatively, Smithwick, 1949 [13], has shown that there is a definite tendency of blood pressure to return to and toward pre-operative levels with the passage of time following sympathectomy. These points are illustrated by the comparison of the blood-pressure levels

TABLE II

Comparison in previously unoperated patients of the lowest blood-pressure level during differential spinal block with resting levels and levels during sedation before operation, and with resting levels immediately after operation and twelve to twenty-six months post-operative.

					B.P. levels before operation			B.P. levels after operation		
Name	Sex	Age	Type	Operation	Resting	Sedation	D.S.B.	2 weeks	12 months	18–26 months
H. P.	M	36	I	L.D. spl.	211/162	146/88	150/94	144/98	147/107	170/102
E. G.	F	34	I	L.D. spl.	200/140	160/100	120/95	167/119		104/86
J. R.	M	54	II	L.D. spl.	206/132	175/110	148/106	175/113	169/118	186/122
M. E.	F	51	II	L.D. spl.	182/107	90/50	112/75	151/100	152/91	
E. P.	F	50		L.D. spl.	230/135	155/85	118/79	163/88	146/86	
E. E.	F	50	III	L.D. spl.	229/130	140/95	140/80	213/116		
A. F.	M	34	I	L.D. spl.	178/120	130/100	140/95	140/86		150/95
M. T.	F	51	III	L.D. spl.	187/102	130/80	141/79	192/110		196/100
M. S.	F	52	III	T.T.D. spl.	230/130	165/110	174/100	189/95	203/108	177/82
R. C.	F	48	I	T.T.D. spl.	158/129	130/81	95/75	192/130	152/103	
L. S.	F	39	III	None	219/166	160/110	190/110			
J. K.	F	53	II	None	211/136	200/110	174/111			
M. C.	F	42		None	140/80	90/70	100/70			

TABLE III

Comparison in 5 patients who had previously undergone sympathectomy of the lowest blood pressure during differential spinal block with resting levels and levels during sedation before operation, and with resting levels immediately after operation and twelve to thirty months post-operative.

						B.P. levels before 2nd op.			B.P. levels after op.		
Name	Sex	Age	Type	Prev. Op.	2nd Op.	Supine	Sedation	D.S.B.	Immediate	12 months	24–30 months
H. R.	M	42	II	L.D.	T.T.D.	194/138	136/80	180/130	181/114	155/102	169/107
A. S.	F	44	II	Peet	T.T.D.	184/126	145/104	180/114	218/126	188/116	
C. C.	M	26	I	L.D.	T.T.D.	141/108	134/106	130/95	122/93		
A. C.	F	27	II	L.D.	T.T.D.	176/123	148/90	135/105	120/78		
O. D.	M	51	II	L.D.	None	206/118	140/78	166/100	Rice diet 149/100	198/125	213/140

in patients in the course of differential spinal block with their resting levels, the levels under sedation, and levels following operation after a period of from one to three years. Table II presents a summary of these data in a group of patients who were being studied for the purpose of evaluation with a view to surgery. Table III is a summary of similar studies in a group of patients who have previously undergone lumbodorsal splanchnicectomy and in whom additional denervation was being considered. It is evident that blood-pressure level during differential spinal block does not consistently indicate the level which will result from operation, either early following operation, or one to three years later. These results serve to emphasize the statement already made that any type of regional block in the evaluation of hypertensive patients furnishes only one item of information, namely that the blood-pressure level in a given individual may or may not be temporarily reduced by the interruption of impulses from the autonomic nervous system. This information may be of considerable value in certain individuals, but it cannot be used as a criterion for deciding the advisability of operation in a given patient.

Russek, Southworth, and Zohman, 1948 [14], have recommended the use of caudal block not only for the selection of patients for sympathectomy, but also for the purpose of determining the extent of denervation indicated in the individual case. From a technical standpoint it is difficult to determine the exact level of sympathetic effect of any regional block to correlate it with the blood-pressure level at a given moment. It has not been possible to work out any method by which the exact level of the extent of sympathetic block in the lower and middle thoracic segments can be determined. Skin temperature readings on the trunk cannot be used for this purpose, and in many cases the level of diminution of appreciation of pin-prick does not correspond to the level of sympathetic denervation. It is our observation that the dermometer readings indicating changes in skin resistance are erratic and unsatisfactory for following exactly the effect of a regional block. It has been our hope that the skin potentials would prove accurate and sensitive enough for this purpose, but up to the present time apparatus for the application of this method has not become available. Because of these technical difficulties, it has not been possible to correlate exactly the extent of hypotension with the level of sympathetic decentralization. In any event, other considerations such as the condition of the cardiovascular system, and the history in regard to cerebrovascular accidents are of more importance in determining the level and extent of sympathectomy than is the fall in blood pressure which results from any type of temporary interruption of autonomic vasomotor impulses, especially since the level of blood pressure which results from any acute procedure is not a valid indication of the ultimate result of sympathectomy.

Because of the complexity of the problems involved, the selection of hypertensive patients for surgery of the autonomic nervous system by methods of regional blocking alone is inadvisable. These methods may be of value for use in certain individuals when the relative importance of the neurogenic factor in the production of the hypertension is in question. For this purpose differential spinal block is the method of choice. Its effects spare the skeletal muscles making it possible to produce even total sympathetic block without causing respiratory paralysis, and the block recedes promptly as soon as the infusion is stopped so that the duration of the induced hypotension is limited.

Abstract

Differential spinal block is produced by the continuous subarachnoid infusion of a dilute solution of procaine hydrochloride. This results in the selective paralysis of the small unmyelinated nerve fibres. The groups of fibres affected include autonomic vasoconstrictor fibres, as well as certain small pain fibres. The use of the techniques of regional nerve block for the purpose of selecting hypertensive patients for surgery of the autonomic nervous system has been recommended by several workers. Differential spinal block produces paralysis of sympathetic vasoconstrictor fibres to a segment as high as the block extends, and causes a fall in blood pressure comparable to that which is caused by a complete spinal block to the same level. Its effects have been observed in 25 patients who were later subjected to the operation of splanchnicectomy. Immediate results of the block compared with the result of operation immediately and after twelve and twenty-four months are described.

It is concluded that the method may be of value in certain cases. Its chief advantage is that a total block of vasoconstrictor fibres may be produced without any respiratory paralysis. In the evaluation of the hypertensive patient for surgery, response in terms of fall in blood pressure resulting from any type of regional block is only one of many factors to be considered.

Resume.—Le bloc spinal différentiel se produit par l'injection continue sous-arachnoïdienne d'une solution fortement diluée de chlorhydrate de procaïne. Ceci paralyse électivement

les petites fibres non myélinées. Parmi les groupes de fibres atteints se trouvent des vasoconstricteurs autonomes ainsi que certaines petites fibres transmettant la douleur. Plusieurs auteurs ont recommandé l'emploi des techniques de bloc nerveux régional comme moyen de sélectionner les hypertensifs qui pourraient bénéficier d'une intervention sur le sympathique. Le bloc spinal différentiel paralyse les vasoconstricteurs sympathiques jusqu'à un segment au niveau atteint par le bloc, et produit une chute de tension artérielle comparable à celle produite par un bloc spinal complet au même niveau. Ses effets ont été observés chez 25 malades qui ont plus tard subi une splanchnicectomie. Les résultats immédiats du bloc sont comparés aux résultats immédiatement après l'opération et au bout de 12 et 24 mois.

L'auteur conclue que cette méthode peut être utile dans certains cas. Son grand avantage est de permettre de bloquer complètement les fibres vasoconstrictrices sans produire de paralysie respiratoire. Toutefois, la chute de la tension artérielle comme suite à un bloc régional quelconque n'est qu'un des facteurs qui doivent être considérés dans l'évaluation d'un malade hypertensif en vue d'un traitement chirurgical.

RESUMEN.—El bloque espinal diferencial se produce por una infusión subaracnoidea continua de una solución de novocaina. El resultado de esto es una paralisis selectiva de las fibras amedulares. Los grupos de fibras afectadas incluyen las autonomico vaso-constrictoras asi como tambien pequeñas fibras de dolor. El uso de las tecnicas de bloque nervioso regional con el proposito de seleccionar pacientes hipertensos para cirujia del sistema nervioso autonomico ha sido recomendado por varios autores. El bloque espinal diferencial produce la paralisis de las fibras vasoconstrictoras del simpatico hasta un segmento tan alto como aquel hasta el cual se extiende el bloque y causa un decrecimiento de la presion sanguinea semejante al causado por el bloque espinal total al mismo nivel. Los efectos del bloque diferencial han sido estudiados en venticinco pacientes en los cuales mas tarde se llevo a cabo la esplanicectomia. Se describen los resultados inmediatos, comparados con el resultado de la operación a continuación de ésta y despues de doce y veticuatro meses.

Se concluye que el método puede ser de valor en ciertos casos. Su ventaja principal es el que un bloque total de las fibras vaso-constrictoras puede producirse sin ninguna paralisis respiratoria. En la evaluacion de el paciente hipertenso para cirujia, el comportamiento de éste en terminos de decrecimiento de presión sanguinea resultante de cualquier bloque regional, es solamente uno de los muchos factores que deben considerarse.

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The paper by Dr. John Lockett on **The Incidence of Hypotension Following Induction with Thiopentone, and Its Prevention by the Use of Methedrine** is to be published in *Anæsthesia*.

Section of Medicine

President—Sir ADOLPHE ABRAHAMS, O.B.E., M.A., M.D., F.R.C.P.

[*April* 25, 1950]

DISCUSSION ON THE PROBLEMS OF OLD AGE

Professor A. P. Thomson, University of Birmingham: The most pressing problems of old age are poverty, solitude and infirmity due to years and chronic sickness. Poverty and loneliness no doubt are problems which concern social policy more directly than medicine but physicians would be unwise to ignore their influence in begetting the degeneration of personality which so often accompanies the advent of senility. It is strange, however, that the problems of chronic sickness in the elderly have attracted so little attention in the past; in a period of rapid therapeutic advance clinicians, with a few distinguished exceptions, have permitted them to languish in neglect. For this misfortune there are three reasons; first, the care of the aged and infirm lacks the dramatic appeal of acute illness in the young; second, complete recovery is rarely possible and the result often seems disproportionate to the effort required and, lastly, these patients have been segregated in vast infirmaries poorly staffed and ill-equipped with laboratories and other departments necessary for satisfactory investigation and research. By faulty and unimaginative administration the maladies of the old have been removed from the common stream of medicine with consequences disastrous not only to the patients but to the growth of knowledge itself.

My responsibility as Chairman of the Planning Committee of the Birmingham Regional Hospital Board compelled me to interest myself in this matter just over two years ago. Dr. Marjorie Warren had shown that by active and suitable treatment much might be done to help the elderly and infirm and Lord Amulree had devoted attention to the improvement of the infirmaries but no detailed statistical study had been made of the patients, and our first work was a comprehensive investigation of the inmates of a large institution in Birmingham and of others in Stoke-on-Trent.

The preliminary results were published in the Lumleian Lectures last year and a complete analysis of them is available in a series of five papers from my colleagues Professor T. McKeown and Dr. C. R. Lowe of the Department of Social Medicine in the University of Birmingham. We found that no less than three-fifths of the patients did not require hospital treatment at all; that is they had no need of skilled nursing or frequent medical attention. They occupied beds because they were either homeless or had no relations or friends able and willing to care for them and they could not be discharged in such circumstances because in the apathy of prolonged institutional life they had lost all initiative and desire to accept responsibility for the ordering of their own lives. It was impossible to determine accurately the condition of the patients at the time of their admission but it was clear that many of them had entered the hospital as the result of some domestic catastrophe rather than as a consequence of illness.

I decided therefore that a further investigation was necessary and that an analysis of an adequate number of patients applying for admission to the Infirmary must be undertaken. By the co-operation of five physicians (Hearn, G., ; May, K.; Marson, F. G.; Nagley, L.; Thomson, A. P.) and an almoner, Mrs. Sagrott, who was helped by the almoners of the University Hospital, we made a clinical and social study of 393 consecutive applications for admission to Western Road Infirmary from October 10 to December 22, 1949. These patients were examined either in their own homes or immediately after admission and the social and domestic survey is based on a comprehensive study by the almoners.

Of the 393 patients 32 (8%) refused admission when they discovered that they were destined for what they still considered to be a workhouse. By making various domestic adjustments, including the provision of home helps and district nursing, it was possible to provide accommodation for them with relatives. Four of this group (two in the wards of a general hospital and two in their own homes) complained that no one had told them anything about the proposed transfer. In addition no less than 20 patients died before they could be examined—that is within two days of the receipt of the request for admission—and six others were admitted to general hospitals. The number for statistical analysis was thus reduced to 335 (161 men and 174 women). Of this total 90% were over 60 years of age and 66% were 70 years or over.

Clinical classification.—The frequent association of several apparently distinct pathological conditions in a single patient makes clinical classification of the senile extremely difficult. In recording our opinions during the survey we placed first, as the essential diagnosis, the condition that seemed to contribute most urgently to the general disability that required removal to hospital. It is worth notice that 46 patients had obvious malignant disease and that 19 others were suspected of it and recommended for admission for investigation. Together this group of 65 (20%) was the largest and the figure surprised us until we remembered that in the Registrar-General's returns (1945–7) no less than 15% of all deaths over 60 years of age are attributed to malignant growths.

Domestic structure.—One-third of all the patients were living alone in the sense that they had no frequent contact with relatives and for human companionship were dependent on neighbours, casual acquaintances or fellow inmates of lodging houses and municipal homes. In addition 22% of the men and 12% of the women were living in isolation with a spouse.

These figures are very much higher than those quoted by Sheldon (1948) in respect of the general condition of old people in Wolverhampton where only 17% were reported by the social survey to be living alone and there was good reason to suppose that this figure was excessive.

Just over one-half of the women (52%) were living with children or other relatives; the comparable figure for men was 44%.

Housing.—28 patients came from municipal homes or common lodging houses and one was admitted from the street, homeless because he had been turned out of his lodgings. This part of the survey is based therefore on an examination of 306 dwellings.

In 21 houses (7%) there was no internal water supply; a tap in the yard sufficed. Only 63 (21%) had any arrangements for the ready supply of hot water and many of these were unsatisfactory and dependent on decadent geysers.

Two hundred and twenty-two houses (72%) had no bath and in 24 the bath was supplied with cold water only and before it could be used by an invalid it was necessary to fill it with kettles from the gas cooker or fire.

Only 62 houses (20%) had indoor sanitation. Of the 244 with outdoor accommodation (80%) no less than 90 (30%) shared it with neighbours. The "back to back" houses numbered 63 (21%).

A general housing survey was made in Birmingham in 1946 and I have abstracted certain figures from it for comparison with those of our selected group.

	General Housing Survey 1946	Houses of patients applying for admission to infirmary 1949
No internal water supply . .	2·25%	7%
No bath	29·00%	72%
Shared outdoor sanitation	12·25%	30%
Back to back houses . .	10·00%	21%

It is obvious that the housing conditions of the applicants to the infirmary in 1949 were much worse than the general average in Birmingham in 1946.

Overcrowding.—The legal definition of overcrowding is expressed in the Housing Act of 1936 as any excess of population above the following scale:

To 1 room, 2 persons; 2 rooms, 3 persons; 3 rooms, 5 persons; 4 rooms 7½ persons. There is a proviso that any room to accommodate two persons must have a minimum floor area of 110 square feet.

Living rooms are included in the total available and, for the purposes of the Act, an infant less than a year old does not count as a person but a child under 10 is to be reckoned as half an adult. The mathematics of the Housing Act rest on very dubious assumptions; in a small room an infant may loom somewhat larger than the bulkiest adult. On the present standard a four-roomed house may accommodate without legal overcrowding a family made up of grannie and grandpa, father and mother, one child over 10, five children under that age and a baby—in all 7½ persons for the purpose of the Act but eleven human souls nevertheless.

By these stringent standards 1·92% of all the houses in Birmingham were deemed overcrowded in 1946. If living rooms were excluded from the computation and not regarded as bedrooms the figure rose to 11·25%. In our survey on the same basis it was 17% but we took no account of the size of the bedrooms, many of which were difficult to enter and certainly had floor areas less than 110 square feet.

Two examples of conditions not rare in our experience may be quoted:

(1) Back-to-back house, one room up and one down with an attic used as a bedroom which certainly would not have won the approval of the Royal Society for the Prevention of Cruelty to Animals as a kennel for pets. Shared outside sanitation, no bath, no hot water.

Single man in terminal stages of congestive cardiac failure living with married niece, her husband and five children. The patient sleeps in the only downstairs room on two chairs; the married couple and the children in the rooms above.

(2) Slum house: one room down, two up (including attic), no bath, shared outside sanitation. Old lady, a widow, of 81 years with severe abdominal pain due to partial obstruction with visible peristalsis, living with married daughter, son-in-law, two adult children and another under 10. The patient shared a bedroom with her daughter, son-in-law and 6-year-old granddaughter.

In 205 (67%) of the houses visited the sick were in separate bedrooms but in 35 cases this was a euphemism for the exclusive use of the living room at night. 101 of the old people shared a bedroom; 34 of these were partnered by someone other than a spouse. 72 of the patients were sharing a double bed and of these 26 were incontinent.

These grim and sordid facts shocked all of us; we had not thought that life in England now could be so hard, so dreary and so desolate as, with but few exceptions, we found it for the aged sick we visited at home. Their sufferings have no tongue; they are borne in silence in dark, infested slums.

To work in the survey was depressing; all of us felt a curious sense of guilt as if we were responsible (as perhaps in part we were) for the misery before us. Two things lightened the dismal tale: first the courage and endurance of the patients and their gratitude, and second the astonishing kindliness, charity and devotion with which these poor people were tended by neighbours, friends and relatives. That they should be merely visited and examined, that they could feel for a moment that they were not completely forgotten was to most of the patients a source of genuine pleasure—they welcomed us even when we made it clear that we could promise them no substantial help immediately. Most of them had been ill for a long time, many of them for years and yet they clung to their homes until they were overwhelmed. General statements fail in description of the tragedy encountered and particulars of individual cases convey it better.

(1) A woman of 89; very ill for two months and not well for some time previously. Consolidation of the right base, possibly unresolved pneumonia, possibly bronchial obstruction. Incoherent and obviously near death. History from her companion, a woman in the forties. "She lived two doors away; her husband died thirteen years ago so I began to look after her and got to like her. During the 'blitz' she was frightened and my husband and I used to bring her in here. I have four children and when the youngest came I couldn't get in to see her so we brought her here to live and she stayed. As the children got bigger we were very crowded and so she went to live with her daughter but was unhappy. One night about a year ago we found her sitting outside on the step crying and saying that no one wanted her. So of course we took her back and she was happy until she got very ill seven weeks ago. I have nursed her since. It is very difficult because three children sleep in her room and my husband is worried lest she might die in front of them."

There were only two bedrooms and one tiny attic occupied by the oldest child.

(2) A woman aged 81; failing for some years; restless and irritable since a slight stroke three months ago; liable to fall and has to be looked after all the time; sharing a bedroom with daughter and son-in-law. The latter has done night work continuously for three months so that he might help to care for her by day while his wife did her work and saw to the four children.

(3) A woman of 41 with five children. In 1940 a bomb shattered part of the house; she had difficulty in walking afterwards and was found to have disseminated sclerosis. A little later another bomb killed three relatives close by and she was worse.

For five years she had been sitting night and day in a wooden chair in the living room because she could not walk or be carried to bed. Both legs were grossly œdematous (apparently due to the immobility) and urine was trickling down them. If she tried to put clothes on she got violent clonus and she found that this was less likely to occur if her legs were very cold and covered only by a thin blanket. For the same reason she liked her heels to rest on a folded sack with the bare toes on the stone floor. There was a huge pressure sore on the buttocks and the sacrum was in contact with the seat of the chair. She was in great pain and died of septicæmia two days later just after reaching hospital. When I asked her why she had not applied for admission earlier, she said: "Every woman likes to be with her children as they grow up—but I can't help them any more."

Nobody had ever suggested a district nurse or domestic help.

Such cases were not exceptional; they were common. We were all convinced that there was no abuse of the infirmary; that admissions in the past had been justified because no other method of relief was possible. The laments from social workers about loss of morale and the decline of family cohesion and the sense of social and neighbourly responsibility are not warranted by our experience. In the light of what we saw the precise opposite was more often true.

Disposal.—The main purpose of our recent survey was to determine what proportion of the patients applying for admission to the infirmary required hospital treatment and, to this end, we recorded our opinion as to the proper disposal of each case with the following result:

Group 1.	Requiring admission to hospital	136	40%
Group 2.	Requiring admission to mental hospital	34	10%
Group 3.	Requiring admission to a "hostel" (an institution in which simple nursing and domestic care were available)	79	24%
Group 4.	Best treated at home with the aid of district nurses and social services to be provided by the Local Authority	86	26%
	Total	335	100%

In the first group (requiring admission to hospital) we placed all cases of recent hemiplegia and malignant disease causing severe pain.

As the standards of the five physicians who took part in the work might vary we each of us reviewed the reports of our colleagues and made independent recommendations for the disposal of patients we had not personally seen (and without knowledge of the prior decision). With regard to groups 1 and 2 there was remarkable agreement and we can therefore be confident that of all applications for admission to the infirmary (neglecting those that withdrew their applications and those that died or gained admission to other hospitals—in all 58) only 40% required it and 10% should be admitted to mental institutions. From the point of view of administration this is the most important result.

In groups 3 and 4 the cross check revealed considerable divergence of opinion and no final decision is possible. Experience of the value of the help to be supplied by Local Authorities in the patients' homes will in future enable us to estimate more accurately the number of beds required in institutions for custodial care and simple nursing.

The statistical data available are so scanty that it is impossible to apply the results of the Birmingham surveys to the national problem as a whole. It is known that there are about 5 million people in Great Britain above the age of 65. Of these roughly 150,000 (3%) are accommodated in institutions of one kind or another. With reference to the 70,000 infirmary beds in this total we are confident that the majority are occupied by patients who do not need that sort of provision. In other words there is no reason to expand infirmary accommodation now; the immediate necessities are better houses and the provision of nursing and domestic help in them, the establishment of simple hostels for custodial care, improvement in the staffing and equipment of infirmaries to deal with the patients they admit and the extension of accommodation for the cases of mild senile dementia. That is the position to-day but it would be folly to ignore the fact that if present trends continue the number of persons over 65 in Great Britain in 1975 will be 8·5 millions and not 5 millions and the social problem of old age for our successors may well be the most difficult of any that threaten Western civilization.

Relation of the study of the aged to clinical medicine.—Within the past thirty years there have emerged two distinct challenges to clinical leadership in the treatment of the sick. The first is in the development of the technique of social medicine in the study of the group, the growth of the science of human ecology for which Ryle at Oxford and Spence in Newcastle have done so much. The second is the ever-increasing application of the methods of exact science to the problems of diagnosis and control of treatment.

They are both respectable challenges to be welcomed by the wise and not lightly to be put aside by the aggressive self-confidence of the practical man.

From social medicine we discover the relative importance of different aspects of disease and from the exact sciences we have learned the fallacies that attend speculations and conclusions based on clinical impression. Rapid development of new techniques involves the danger of departmental specialism, the intensive study of a system rather than the contemplation of the whole and individual man.

Whether it is reasonable to hope that the methods of exact physical science will ultimately express the true nature of biological phenomena is a topic on which philosophers differ. Schrödinger has pointed out that the seemingly immutable order of physical and chemical reactions is in essence an average statistical result derived from the study of enormous numbers of atoms whose individual behaviour may be quite disorderly. The puzzling thing in biology is that a particle so small as a gene—occupying space sufficient for 100 to 150 atom distances and far too small for statistical accuracy—should nevertheless maintain its integrity over long periods of time.

The scientist proceeds by a method of abstraction; from the totality of things he isolates a group or single entity and places it in an artificial environment free from what is considered to be irrelevant interference from the whole environment and there studies its reactions with other substances or forces similarly abstracted. The pragmatic success of the method is its

justification but is it applicable to clinical medicine? In part certainly but not I believe entirely. It is for instance impossible to abstract a human being from his environment for dispassionate study in a laboratory; his memories, his past experience, his fears, his hopes and his desires attend him; we cannot part him from them and they all affect his reaction to the tests that we apply.

There is also the inexorable prerogative of ethics; no physician may be indifferent to the fate of the material with which he works—even if it be old.

These general considerations are fascinating but there are more practical reasons why clinicians should take an interest in the aged. The elderly are often excellent material for an exercise in clinical taxonomy; a single patient may be a veritable museum of pathological phenomena and rarely is a single diagnosis possible. By the study of them we may increase our knowledge of the natural history of disease, improve prognosis and reach a more accurate assessment of the value of therapy. Most important of all, perhaps, is the simple fact that it is a duty that clinical medicine owes to a society confronted with a radical change in its age structure. Our task is to learn how to give vitality and significance to the later years of human life and we can discharge it only by patient study of all aspects of the problem.

The clinical and sociological surveys that we have made in Birmingham have revealed not only the measure of the difficulties but also some errors in the administrative approach to them in the past which may now be corrected.

Dr. F. G. W. Marson will describe some of our first steps in closer analysis of the phenomena of ageing and I wish to emphasize how wide is the field of study; it demands not only clinical competence at the bedside but an ability to understand the lessons of social medicine and the technique of the laboratories. In my view it transcends any narrow specialism and the term geriatrics should be forgotten. The task is one for general physicians able to compare what is found in the later stages of life with what has gone before.

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Lord Amulree: To-day about 70,000 beds are occupied by the "chronic sick" of whom the majority, about 85%, are elderly.

I share Thomson's belief that a large number of the 70,000 beds are occupied by people who need not be there: certainly this is true for the elderly folk, I am not in so good a position to speak of the younger. This has been the general experience of anybody who has come to work in a "chronic sick" hospital, or wards of a hospital, and has made any attempt to assess the needs of the patients. There is the classic example of the West Middlesex Hospital (Warren, Margery (1948) Evolution of a Geriatric Unit from a Public Assistance Institution, *Proc. R. Soc. Med.*, **41**, 337).

My own experience at St. Pancras has shown that fifteen months after the establishment of a special department containing 130 beds to look after these elderly patients, there are now 54 persons, or 42% of the whole, remaining in hospital who do not need hospital treatment. These patients can be divided roughly into two categories:

(1) Those admitted before July 5, 1948.
(2) Those admitted after July 5, 1948.

The importance of this date lies in the fact that on it St. Pancras Hospital became part of University College Hospital, although the department to which I have referred did not begin work until January 1, 1949.

It is to be hoped that the disposal of patients admitted after July 5, 1948, will not be so difficult as it has been for those admitted before that date for two reasons:

(1) Many of these new patients should not need to stay in hospital for so long a time. One report that I read recently recorded that a reduction of stay in hospital from an average of over 260 days to one of under 100 days could be obtained from employing more active treatment. In my own experience, with 75 admissions during the past fifteen months, the average stay in hospital, including deaths, is fifty days, and if disposal were easier it could probably be reduced below that figure.

(2) The patients, and their relatives—this latter is most important—will be encouraged, from the start, in the belief that the proposed stay in hospital will be short, and that the patient will soon be coming home again.

This attitude will, it is hoped, help to stop the practice of relatives disposing of their elderly connection's room and belongings when he or she is admitted to hospital. It will

not, however, discourage the type of person, happily not very common, who sells up all that he has and who arrives at the hospital door almost saying: "Here I am, keep me for the rest of my life".

Local authorities can supply many services, home helps, home nursing, meals, &c., which will enable elderly persons to continue to live in their own homes. Although these services are costly, this cost compares favourably with that of maintaining a patient for months, or may be for years, in the hospital. The elderly patient who lives alone gives rise to particular difficulty. According to the Rowntree Report the proportion of these in the country varies from 18% of all single elderly persons in a London borough to 1% in the Mid-Rhondda Valley. Too often there comes a time when home helps, &c., are not enough to keep the patient comfortable in his own home.

I should like to give two examples of the difficulty that may arise with these patients:

(1) An old lady of about 79 lived alone in a small three-roomed flat. The neighbours complained to the Town Hall that the conditions under which she lived were insanitary, the M.O.H. called on her and asked me to see her. I went round with one of my colleagues and found that the old lady was nearly blind and that she had worn no shoes or stockings for over six months because she could not bend down to put them on. Her feet and legs were red, œdematous and filthy. She had slept on a chair in the kitchen for an uncertain period of time, and one jet of the gas cooker was kept permanently alight: the flat was filthy, but the pan of the W.C. was clean—this gave me some hope for the future. She was mentally confused, and complained of the Communists coming down the chimney and interfering with her wireless. She was persuaded to come into hospital, and was found to be suffering from a double cataract and to have her left leg 4 in. shorter than the right due to an old fracture of the hip. One cataract was extracted, and she is waiting to have the other operated upon. Shortly after admission her mental confusion cleared up, and no more was heard of the Communists. She is now clean and tidy, with a normal mind and some vision. It is unlikely that she will be able to go back to her flat, and, as she has turned out to be a well-educated woman it seems wrong to send her to an institution. What, then, is to become of her?

(2) An old lady of 85 who lived alone in a room on the top floor of a London house. She was nearly blind, and was visited by a welfare worker for the blind. Her neighbours reported to the Town Hall that "something was wrong" and, after making an investigation, the M.O.H. asked if we could admit her. Two of my colleagues visited her, and found her lying on the floor with her head in the grate, covered with soot: she appeared quite deaf and blind. She was admitted to hospital, where for one week she had to be artificially fed. She soon improved, and is now quite a cheerful, active old lady—hard of hearing, but not really deaf. Her only complaint is that we do nothing to make her see better, but unfortunately, she suffers from macular degeneration, for which there seems to be no remedy.

Again, what is to become of her? She is too blind for admission to an institution, and the few Homes for the Blind have long waiting lists.

These people, and there are many of them, fall in between the two Acts—National Health and National Assistance. Some few people foresaw this difficulty when the two Bills were before Parliament, but they were assured that all would be for the best in the coming Brave New World. There is urgent need for the provision of accommodation for these people who are rejected by the National Health Act as being too well, and who are yet not well enough to go into the accommodation provided for healthy old people under the National Assistance Act. They require care and attention, and should be covered by Part III of the National Assistance Act, which enables Local Authorities to provide accommodation for people who, by reason of age or infirmity are unable to look after themselves. But the accommodation that has been provided hitherto under this section has been for people who could be transferred thither from the workhouse, or institution, in other words, for people who are fit enough to lead an independent life, with some one to provide the housekeeping facilities. Something wider and more comprehensive is required.

Another problem related to this is that of the Long Stay Annexe. This accommodation is intended for those patients who, after having been thoroughly examined and treated in hospital, are pronounced to be really incurable, and who will, therefore, need to be under permanent medical and nursing supervision. It is important to keep these patients under a fairly strict control from the central unit where they have already been investigated and treated. One can never be sure when the apparently irremediable will become remediable. For example, if Compound E were to become widely available, many patients whose condition is at present considered to be irremediable would become amenable to treatment, and no longer suitable for retaining in a Long Stay Annexe. To a less spectacular degree, this same argument may apply to other types of patient. For example, I have a patient, a woman of 67, who had a stroke in 1926 and another in 1946. She had been in hospital since this last stroke. She has a left hemiplegia, is mentally alert, and weighs about 15 stone. When

we first took over, she was marked down as one of the more promising patients. But for over a year she made no progress, she was placed in a chair for a certain time each day, but that was as far as we got until a new Sister was appointed to the ward, and the position of the patient's bed in the ward was altered. But about six weeks ago the patient decided to learn to stand up and can now walk, with help, a few hesitant steps.

I quote this example to emphasize that the Long Stay Annexe can develop into the worst type of Poor Law dump—agreeable but dangerous, and the more dangerous because it will be more agreeable.

It looks as if the efforts of the medical profession will in a short time have outrun the efforts made by the community to take care of the aged suitably and economically. Should medicine therefore, stop? Or should the community be encouraged, rather than forced, to accept its added responsibility? I hope, but I am not sure, that the answer to this question will be the correct one.

Dr. F. G. W. Marson, Birmingham General Hospital: In the medical study of the elderly one aspect is to determine the biochemical changes as compared with younger groups. Given these changes, what factors in the elderly have produced them, and what significance may they have to the well-being of these persons?

In a lecture to the American College of Physicians in 1947, Albright mentioned the term "adrenopause". By this term, he meant a progressive diminution in production of certain adreno-cortical hormones, commencing at various ages between 60 to 90 years. He cited as proof of its existence, the fact that very elderly women have scanty axillary and pubic hair, and very low 17-ketosteroid excretions in the urine.

It is with this term "adrenopause" in mind that the following investigations have recently been started. This is merely a preliminary and incomplete communication.

Although the cases investigated were necessarily patients in either Dudley Road Infirmary or Birmingham General Hospital, they have been restricted to those cases whose pathological conditions do not normally alter the investigation results. The ages have varied from 60 years upwards.

(1) *Axillary hair and 17-ketosteroids.*—In confirmation of Albright's remark, 100 consecutive female patients revealed that 40 cases had no axillary hair at all and only 13 cases had more than 50 per axilla.

I think it is generally recognized to-day that the 17-ketosteroid urinary excretion decreases with advancing years, and starts falling at about 50 years of age (Callow and Crooke, 1944; Barrett *et al.*, 1946). In females, the adrenal cortex is the only source of 17-ketosteroids, whereas in males it is believed that the adrenal cortex is responsible for about two-thirds of the total, and the testes for the remaining third. The daily output for normal adult men and women is said to be about 15 mg. and 12 mg. respectively. The 17-ketosteroids were estimated in eight females and thirteen males, all over 70 years of age. The males averaged about 4 mg. (range 2·0–7·7) and the females 2·4 mg. (range 1–5).

(2) *Sodium, chloride and potassium.*—These electrolytes were estimated in 50 cases.

The chloride figures ranged from 333–399 mg.% and gave a mean value of 370 (normal 340–376 mg.%).

The potassium figures ranged from 14·8–24·2 mg.% and gave a mean value of 19·3 (normal 16–22 mg.%).

The sodium figures are the ones of interest. They ranged from 296–340 mg.% and gave a mean value of 319·7 (normal 320–350 mg.%). Of the 57 sodiums estimated 28 were below the 320 mg. mark. Some of the lower figures were repeated twice and thrice, and were consistently low.

From these figures, it would appear that the range of sodium in the elderly is distinctly lower than the range in younger people. Obviously this number of cases is small, sodium estimations being such a laborious process. If these figures can be confirmed with a much larger series, the significance may be of some import.

Blood levels of sodium and chloride do not always run a parallel course (Goldzieher and Stone, 1949). Certainly in many of these elderly cases the expression of chloride concentration as mg.% of sodium chloride would have been fallacious.

I would like to mention at this point that although we regard the adrenal cortex as the controller of the sodium chloride balance, determining excretion in urine and sweat, any of these low sodiums can be readily raised to normal by testosterone or stilbœstrol. Such therapy, in my experience, raises the sodium without affecting the chloride levels. Lack of œstrin and testosterone in this age-group might reasonably be expected to diminish the power of sodium retention.

The sodium ion is the more important from the osmotic standpoint, and a significant fall in the serum value may indicate a gross total deficit. Prior to such fall, the kidneys would

normally excrete water in the attempt to maintain extracellular isotonicity. A low serum sodium figure might therefore be expected to be accompanied by a diminished extracellular fluid volume.

Such a state of affairs would prejudice the chances of the elderly in such conditions as diarrhœa, diabetic coma and heat exhaustion. It is interesting to note that in a series of 8 cases of uræmia induced by Neptal and low salt diet treatment of congestive heart failure, the youngest was 56 years. This complication has not so far been witnessed below this age (Black and Litchfield).

(3) *Insulin sensitivity tests.*—This test was performed on 25 cases, 11 females and 14 males. Each patient had been fasting over sixteen hours, and the insulin dose was calculated at 0·1 unit per kilo body-weight. Blood sugars were estimated in fasting state and at 20, 30, 45, 60, 90 and 120 minutes after the insulin injection.

In no case was the reaction such as to necessitate cutting the test short. The patients' concern was far more with their temporary fast than with any untoward symptoms.

The average figures for these 25 tests, expressed as percentages of the fasting sugar levels were 71, 61, 62, 69, 76 and 84% respectively.

In only 3 cases did the blood sugar return to the fasting level within 120 minutes. In one case the sugar level fell progressively to 43% of the fasting level at 120 minutes, and symptoms were just developing at this stage. Apart from these 4 cases, there was little scatter, and the figures conformed more or less to the mean line. There was no appreciable difference either between the two sexes, or in the decades over 60 years.

The main thing that strikes me about these results is that in 22 of the 25 cases the test results did not conform to the usually accepted normal figures.

The abnormal features seem to be: (*a*) decrease in maximum fall, (*b*) delay in maximum fall, and (*c*) delay in return to fasting level. Although the significance of these findings is not clear, one interpretation might be: (*a*) increased insulin resistance, (*b*) result of lowered basal metabolic rate in the elderly, and (*c*) deficiency of adreno-cortical hormones concerned with gluconeogenesis.

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Dr. W. M. Crofton pointed out that there were always in the skin and the respiratory and intestinal tracts, microbes which were continuously passing into the interior of the body where they constantly assumed their very minute virus phases. These were normally excreted by the kidneys into the urine where they could always be discovered.

It was these microbes in their virus phases that produced the scleroses, cataract, the various rheumatic conditions and misnamed degenerations characteristic of old age. Sometimes an epidemic infection such as influenza, would infect, for instance, the basal ganglia, producing as a sequence palsied old people in their teens.

Dr. George Graham asked Professor Thomson whether he could offer any explanation for the great decrease in the death-rate among elderly people which has taken place since 1940.

Dr. A. J. Bernfield said it must not be thought that geriatrics or the treatment of the aged sick was a new development.

In the so-called Chronic Sick Hospitals which previously were under the control of the London County Council, old people who were ill were treated for their illnesses just as if they were "geriatric problems".

He thought that some of the abnormal biochemical findings in a series of cases of chronic sick presented by Dr. Marson appeared to be within normal limits.

Dr. C. A. Houlder wished to put in a plea for those patients who could not be considered senile but who, because of chronic illness, were forced to share accommodation with senile patients. In this group were found relatively young people who were incapacitated by chronic disorders of the central nervous system, rheumatic diseases and cardiovascular diseases. These patients were usually in full possession of their mental faculties and for many reasons it was undesirable that they should be compelled to spend often many years in an atmosphere of old age and decay. He felt that other arrangements should be made for them.

Professor Thomson, in reply to Dr. George Graham, said he thought that the diminished death-rate among the elderly was due to chemotherapy and the use of antibiotics.

Section of Endocrinology

President—A. S. PARKES, M.A., Sc.D., F.R.S.

[*April* 26, 1950]

Antithyroid Substances in the Treatment of Hyperthyroidism

By Professor D. M. DUNLOP, M.D., F.R.C.P.,
and C. F. ROLLAND, M.B., M.R.C.P.Ed.

(*From the Department of Therapeutics, University of Edinburgh, and the Clinical Laboratory, Royal Infirmary, Edinburgh*)

THE numerous reviews of cases of thyrotoxicosis treated with thiouracil which have hitherto appeared have covered too short a period of time and sometimes have dealt with an inadequate number of cases. Thus, certain questions have necessarily been left unanswered, particularly the question as to the permanency of the remission induced by thiouracil after the use of the drug has been discontinued. We have now had six years clinical experience of thiouracil and certain aspects of the problem seem to be crystallizing out more clearly.

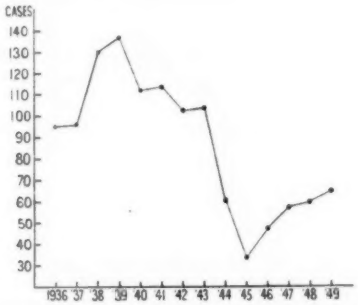


FIG. 1.—Thyroidectomies per year for thyrotoxicosis in Royal Infirmary, Edinburgh, 1936–49.

Fig. 1 shows the number of thyroidectomies for thyrotoxicosis undertaken in the Royal Infirmary of Edinburgh since 1936. It will be seen that the number was increasing steadily before the war. This tendency was checked in 1939, probably due to the outbreak of hostilities, and remained at a fairly constant figure till the dramatic and sharp fall which occurred in 1944 and 1945 following Astwood's introduction of thiouracil into clinical medicine. As the limitations and drawbacks of the treatment have become appreciated, the number of thyroidectomies has slowly risen again, though less than half the number are performed now than was the case in the peak years before the war. The pendulum of medical fashion nearly always swings too far in each direction. Possibly both methods of treatment may be replaced in the future to some extent by radio-iodine, but of this we cannot speak as we have had no clinical experience of the isotope. Thiouracil, if only for its general availability, will have an important role to play for years to come.

This review comprises 200 cases of thyrotoxicosis treated in our charge with thiouracil between 1944 and the middle of 1949. A few more, who have received the drug, have been excluded from the survey because of doubts about the accuracy

of the diagnosis. The cases treated in the last six months have also been excluded as the short period of treatment would have made their study unprofitable.

Thiouracil itself was used in 1944 and 1945 and methyl thiouracil since then. The latter is cheaper and slightly more potent, but otherwise no striking differences have been observed between the two preparations. Only a very few patients have received propyl thiouracil. Because of its reported relative freedom from toxicity it may be the drug of choice, but we have had no extensive experience of its use as it has not been very freely available in this country.

The dosage employed of thiouracil or methyl thiouracil was 0·2 gramme three times a day for three weeks or a month, except for mild cases when this initial dose was given twice instead of three times a day. Thereafter the dose was reduced to a maintenance one of 0·2 gramme daily for severe cases and 0·1 gramme daily for mild cases. After all thyrotoxic signs and symptoms had remained in abeyance for some months, or at the first sign of an increase in the size of the goitre, or of mild hypothyroid symptoms, a further reduction in dosage was made to 0·1 gramme and finally to 0·05 gramme a day.

During 1944 and the first part of 1945 the initial stages of treatment were invariably undertaken in hospital. As we became more familiar with the use of the drug, however, we began to treat patients from the start as ambulant out-patients without interfering with their ordinary avocations. This has been the general rule since 1945, and only severely ill or complicated cases have been admitted to hospital.

It is easy enough to distinguish the two types of thyrotoxicosis in their classical forms: the girl of 22 with exophthalmos and a smooth uniform enlargement of the thyroid on the one hand, and the elderly woman with a nodular goitre, perhaps with auricular fibrillation, and little or no exophthalmos on the other; but one type merges imperceptibly into the other as age increases and an arbitrary division is often impossible; indeed we have found it impossible to classify the cases in this survey into those suffering from smooth or nodular goitres.

The raised B.M.R. of thyrotoxicosis may be satisfactorily controlled by thiouracil. Further, we know that the blood cholesterol concentration tends to be low in untreated hyperthyroidism just as it is high in myxœdema, and taking the average of a number of cases it rises under the influence of thiouracil, but this reading does not contribute a reliable yardstick for the control of treatment since in individual cases there is often little correlation between the blood cholesterol concentration and the progress of the case, which may be gauged more satisfactorily by the ordinary clinical signs and symptoms than by any biochemical test. Of the clinical signs the weight is among the most important, and the average gain in weight of 83 consecutive patients treated with thiouracil for a year reached the surprising total of 9 kg. at the end of six months after which it became stabilized.

The three questions we are concerned with are: (1) In what proportion of cases does thyroid function remain normal after treatment has been discontinued, and how long is it necessary to give the drug before stopping its administration? (2) The nature and frequency of its toxic effects. (3) What are the age-groups or clinical types for which thiouracil is specially suitable or contra-indicated?

In attempting to answer the first question as to the permanency of the remission brought about by thiouracil once treatment is stopped we have excluded from the series of 200 cases those who started treatment after the beginning of 1948. This leaves 128 cases in whom treatment has been stopped for a sufficient length of time to permit of some judgment of the results. Table I shows that relapse occurred in 68 of them, necessitating resumption of treatment. We shall see later the result of resuming treatment in a number of this relapsed group.

Table I suggests that there is some correlation between the length of time the preceding treatment had lasted, and the relapse rate on stopping it. Some workers have

TABLE I.—EFFECT OF STOPPING TREATMENT WITH THIOURACIL IN 128 CASES

DURATION OF THERAPY IN MONTHS	NO. OF CASES	NO. OF RELAPSES	PERIOD BEFORE RELAPSE IN MONTHS	DURATION OF CONTINUING REMISSION IN MONTHS
6–	20	16	$2^{(6)}\ 3^{(5)}\ 4^{(2)}\ 5^{(2)}\ 16^{(1)}$	8 – 60
6 – 12	52	34	$2^{(4)}\ 3^{(8)}\ 4^{(10)}\ 5^{(2)}\ 6^{(5)}\ 9^{(2)}\ 10^{(2)}\ 36^{(1)}$	7 – 67
12 – 18	28	10	$2^{(6)}\ 3^{(2)}\ 4^{(2)}$	6 – 45
18 – 24	10	3	$2^{(2)}\ 3^{(1)}$	10 – 23
24 – 30	12	4	$1^{(1)}\ 5^{(2)}\ 6^{(1)}$	6 – 23
30 – 36	4	1	$3^{(1)}$	6 – 17
36+	2	–	–	6 – 20

Fate of 128 cases of thyrotoxicosis treated with a single course of thiouracil. Cases are arranged in relation to duration of treatment. Column 4 shows the interval in months between completion of treatment and relapse, the bracketed figures being the number of cases in each group. Column 5 indicates the duration of remission in those cases where no relapse has occurred, the figures being the longest and shortest in each group.

denied that there is any relationship between the length of treatment and the length of the subsequent remission, and there is no doubt that in some cases in this series a long remission has occurred after a relatively short period of treatment. On the whole, however, it would seem that patients treated for six months or less show a very high relapse rate, which is less marked in those treated for six or twelve months, and much less for those treated for over a year. This is shown more clearly in Fig. 2.

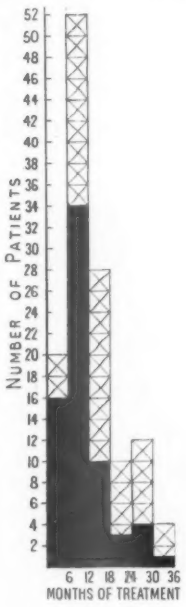


FIG. 2.

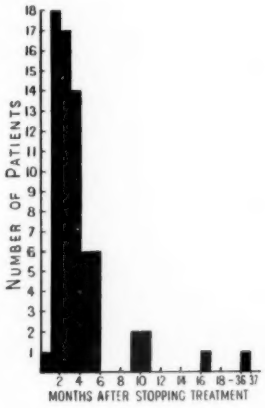


FIG. 3.

FIG. 2.—To show relation between relapse rate and duration of previous thiouracil treatment. Relapsed cases in black. Continuing remissions cross-hatched.

FIG. 3.—Incidence of relapse in relation to time after stopping treatment.

Secondly, the longer the remission the greater the chance of apparent cure; if relapse is going to take place at all it will probably take place within a few months of stopping treatment. This is clearly shown in Fig. 3. The majority relapsed within two to four months of discontinuing thiouracil; only 6 patients relapsed after remaining

well for six months. No doubt some of the 60 patients who have stopped treatment, and who, at the end of periods of time varying from six months to over five years, are at present well, may still relapse, but we cannot help thinking that in most of them a permanent remission has resulted. Almost all of their thyroids have become smaller than at the beginning of treatment, and in the majority there has been a significant recession in the degree of exophthalmos.

Thyrotoxicosis—at any rate certain types of it—is almost certainly a disease in which psyche and soma combine in a disastrous vicious circle. The giving of thiouracil does not liquidate the physician's responsibility to seek for and to try to eliminate psychological stresses and strains. The importance of this as a factor in treatment can hardly be over-emphasized. If, however, in addition the vicious circle can be broken by drug treatment for at least a year on the somatic side as well, strong hopes of a complete cure may be entertained, particularly if the remission is maintained for six months after stopping treatment. Treatment should not be stopped even after a year unless all thyrotoxic signs and symptoms have been entirely controlled by as small a dose as 0·05 gramme daily for some months. We regret that we cannot give any figures showing the incidence of remission in nodular as opposed to primary smooth goitre—our figures include both.

The 68 patients who relapsed were subjected to a further course of treatment for varying periods, and treatment has again been stopped in 26 of them for a long enough time to estimate the relapse rate, which is given in Table II. The numbers are inade-

TABLE II.—EFFECT OF STOPPING FURTHER TREATMENT WITH THIOURACIL IN 26 CASES WHO HAD PREVIOUSLY RELAPSED ON DISCONTINUING TREATMENT

DURATION OF RESUMED THERAPY IN MONTHS	NO. OF CASES	NO. OF RELAPSES	PERIOD BEFORE RELAPSE IN MONTHS	DURATION OF CONTINUING REMISSION IN MONTHS.
6-	2	1	2	10
6 - 12	12	4	3, 4, 5, 9	7 - 36
12 - 18	9	2	5, 6	6 - 17
18 - 24	3	1	2	14

quate to permit of any very dogmatic conclusions being made, but the results follow the same pattern as those shown by the first course, though the number of relapses is smaller—only 8 out of 26 instead of 68 out of 128.

That some patients tend to be refractory to this type of treatment is indicated by the fact that we have 5 patients who have had to have sustained therapy with as large a maintenance dose as 0·2 gramme daily for as long as three years. Any attempt to reduce the dose has resulted in a recrudescence of thyrotoxic signs and symptoms.

The toxic effects we have encountered as the result of thiouracil are shown in Table III. 22 (11%) of the patients have shown a greater or less degree of intolerance to the drug, and in 14 of them (7%) the toxic effects were sufficiently severe to necessitate the abandonment of treatment. In this series there has, however, been no mortality, either from the toxic effects of thiouracil or from uncontrolled thyrotoxicosis. The 3 deaths which have occurred among the 200 patients in six years have been due to causes quite unconnected with their thyrotoxic state.

On the whole, toxic effects were encountered rather more frequently during the initial period of treatment when the patient was taking a large dose, but there were numerous exceptions to this. They were also encountered when a second course

TABLE III.—TOXIC MANIFESTATIONS AMONG 200 PATIENTS TREATED WITH THIOURACIL

	NO. OF CASES	NO. REQUIRING CESSATION OF TREATMENT
AGRANULOCYTOSIS	4	4
LEUCOPENIA	2	1
PURPURA	1	1
DRUG FEVER, VOMITING	5	5
RASHES	5	3
CONJUNCTIVITIS, OEDEMA	5	0
	22 (11 per cent.)	14 (7 per cent.)

of treatment was started after an interval. In out-patients frequent blood counts are quite impracticable as a means of guarding against agranulocytosis, which may be very sudden in its onset. It is therefore our practice simply to give patients definite instructions to stop taking the drug and to report at once should they feel ill, and especially should sore throat, vomiting, fever or skin rash occur.

Slight enlargement of the goitre and mild symptoms of myxœdema due to overdosage were not uncommon, the hypertrophy of the goitre usually preceding the myxœdematous symptoms. They promptly receded when the dose was reduced or treatment stopped. In 2 cases, however, gross accidental overdosage resulted in very large goitres with marked myxœdema. On withholding the drug the myxœdema subsided but not the goitre, which required surgical removal for cosmetic purposes. Two other patients developed moderate exophthalmic ophthalmoplegia which has persisted in both cases in spite of stopping treatment.

Since 1944 only 35 (17·5%) in our series of 200 patients have been subjected to thyroidectomy. In the remainder the results of treatment either continuing or terminated are considered comparable to the results of successful thyroidectomy. 10 of them indeed have had successful pregnancies under "cover" of thiouracil. None of the children was born with a goitre. Table IV shows the reasons for

TABLE IV.—REASONS FOR THYROIDECTOMY IN 35 OUT OF 200 CASES

PLANNED OPERATION		TOXIC REACTIONS TO THIOURACIL		POOR RESPONSE TO THIOURACIL	
LARGE GOITRES	4	BLOOD DYSCRASIAS	5	DRUG RESISTANCE	3
PRESSURE SYMPTOMS	4	SENSITIVITY REACTIONS	4	PERSISTENT FIBRILLATORS	5
RETROSTERNAL GOITRES	2	THIOURACIL GOITRE	2		
UNRELIABLE PATIENTS	3				
PATIENT'S DESIRE	3				

resorting to thyroidectomy in the 35 cases, which gives a fair indication of the type of case which certainly should be operated upon—unsightly goitres, particularly in young and pretty women, goitres causing pressure and goitres which are obviously retrosternal, though the danger of thiouracil causing serious pressure symptoms has been somewhat exaggerated. We do not recall having encountered this as an acute

complication. Some patients are so unreliable and unco-operative that they must be relieved of personal responsibility for their own cure. In addition there will always be certain patients who dislike the idea of continuing drug treatment for an indefinite time. Provided the case is not one of mild thyrotoxicosis with a small goitre in a young person the patient is entitled to some choice in the matter after the advantages and disadvantages of both methods have been thoroughly explained.

Toxic reactions to thiouracil in patients who still required treatment to prevent them from again becoming thyrotoxic necessitated thyroidectomy in 9 cases—the thiouracil goitres already referred to are due to overdosage and not to toxic reactions to the drug. 3 other patients were operated upon because their symptoms did not seem to be controlled by thiouracil in spite of full dosage. It is noteworthy, however, that in 2 of these cases nervousness and tachycardia persisted after thyroidectomy, and it is probable, in spite of their goitres and exophthalmos, that the predominant factor in their cases was a psychological rather than an endocrine one. We believe that true resistance to thiouracil is very rare indeed, if it ever occurs. Lastly, 5 cases were operated upon because of persistent auricular fibrillation, though it is true that normal rhythm might have been attained in 2 of them had quinidine been given, as it was after thyroidectomy. We have insufficient personal experience with thiouracil in auricular fibrillation to compare its efficacy with that of thyroidectomy in this condition. The literature suggests that at least 60% of cases return to normal rhythm in a shorter or longer time under the influence of thiouracil alone, and no doubt a considerably higher proportion is achieved if quinidine is used after the patient's thyrotoxicosis has been controlled by thiouracil. What the corresponding figures are for thyroidectomy and for thyroidectomy plus quinidine we do not know. Table V gives

TABLE V.—11 CASES OF THYROTOXIC FIBRILLATION. RESPONSE TO TREATMENT

CASE	THIOURACIL	THIOURACIL AND QUINIDINE	THYROIDECTOMY	THYROIDECTOMY AND QUINIDINE
1	+ IN 16 DAYS			
2	+ IN 24 DAYS			
3	+ IN 28 DAYS			
4	− AFTER 10 DAYS	+ IN 1 DAY		
5	− AFTER 32 DAYS	+ IN 2 DAYS		
6	− AFTER 42 DAYS	+ IN 2 DAYS		
7	− AFTER 35 DAYS		− AFTER 7 DAYS	+ IN 2 DAYS
8	− AFTER 60 DAYS		− AFTER 7 DAYS	+ IN 3 DAYS
9	− AFTER 95 DAYS	− AFTER 4 DAYS	− AFTER 8 DAYS	− AFTER 4 DAYS
10	− AFTER 36 DAYS		− AFTER 95 DAYS	
11	− AFTER 30 DAYS	− AFTER 4 DAYS	− AFTER 7 DAYS	+ IN 2 DAYS

+ indicates return to normal rhythm. − indicates persistence of fibrillation.

our experience with 11 cases of fibrillation. Three patients returned to normal rhythm once they came under the influence of thiouracil. Three more became normal with thiouracil and quinidine, though case 4 was given an inadequate trial with thiouracil alone which might well have been successful by itself. In 2 cases the fibrillation was resistant to thiouracil and to thyroidectomy but responded to thyroidectomy and quinidine. Quinidine was unfortunately not used with thiouracil in these cases, so that we are unable to make a comparison between the two methods of treatment. Case 9 resisted all forms of treatment, and Case 10 was resistant to thiouracil and thyroidectomy, but quinidine was not employed in this case as she was an elderly

patient with long-standing fibrillation. Case 11, however, responded to thyroidectomy and quinidine after resisting thiouracil and quinidine. One swallow does not make a summer! Had there been other examples of this sort of thing it would have given proof of the superiority of thyroidectomy over thiouracil in this respect.

The possiblity of malignant degeneration occurring in a thyrotoxic adenoma was not regarded as a significant factor in deciding upon thyroidectomy. This possibility is often referred to as an argument in favour of thyroidectomy. We have never encountered malignant change occurring in a thyrotoxic gland but only in non-toxic adenomata, and believe it to be a clinical curiosity in thyrotoxic states.

The problems presented by a large group of thyrotoxic patients vary considerably and the type of therapy selected should take these problems into consideration. Some of the factors deserving attention in the selection of therapy are presented in Table VI, a modified version of a similar table in a paper by Williams (1949).

TABLE VI.—COMPARISON OF THYROIDECTOMY AND THIOURACIL IN TREATMENT OF THYROTOXICOSIS

	THYROIDECTOMY	THIOURACIL
GENERAL AVAILABILITY	−	+
RAPIDITY OF CURE	+	−
TIME LOST FROM WORK	−	+
PERMANENCE OF CURE	+	−
MORTALITY	−	+
GOITRE	+	−
SCARRING	−	+
PRESSURE	+	−
ACUTE EMOTIONAL UPSET	−	+
CHRONIC EMOTIONAL UPSET	+	−
MYXOEDEMA	−	+
CARDIOVASCULAR DAMAGE	+	−
HYPOPARATHYROIDISM AND VOCAL PARALYSIS	−	+

\+ indicates the more desirable form of therapy in respect of each factor.
− indicates the less desirable form of therapy in respect of each factor.

A good thyroidectomist is not always available whereas thiouracil is, and it is a form of treatment which ought to be within the compass of any good general practitioner.

Thyroidectomy usually cures rapidly. Treatment with thiouracil is protracted. On the other hand, thyroidectomy involves about two months off work. Unless the case is severe, or moderately severe, treatment with thiouracil does not necessarily involve any loss of work at all.

The majority of patients are permanently cured by thyroidectomy, though we are a little sceptical that their physical and particularly their psychological state is always as completely satisfactory as some surgeons would have us believe. A considerable number relapse when thiouracil treatment is stopped.

The mortality from thyroidectomy in the hands of the masters is 1% or less, but the overall operative mortality is considerably higher. Death from thiouracil, on the other hand, is exceedingly rare, though some deaths from uncontrolled thyrotoxicosis may occur if the treatment is inefficient.

Unsightly goitres are removed by thyroidectomy in exchange for a scar, which is occasionally unsightly. No scar results from thiouracil but the goitre remains and

may increase in size as the result of overdosage, though it diminishes when a successful remission occurs after stopping the drug.

Pressure symptoms from a goitre are relieved by thyroidectomy but not by thiouracil, which theoretically may make them worse.

An operation is horrifying and psychologically traumatizing to some—long-continued drug treatment frustrating to others.

Myxœdema from thyroidectomy, though easily relieved, is permanent. Myxœdema resulting from overdosage with thiouracil disappears when dosage is stopped or appropriately reduced.

Though thiouracil is undoubtedly of great value in the control of cardiovascular disturbances characteristically associated with the nodular goitre of the more elderly patient, yet there seems to be a general consensus of opinion that thyroidectomy is the treatment of choice in such patients, provided they are not very old. We are in no position to controvert this belief.

Lastly, thiouracil treatment will avoid the complications of hypoparathyroidism and vocal cord paralysis which are admittedly very rare with skilled modern surgical technique, except when a second operation is performed for a recurrence.

We have already considered the definite indications for thyroidectomy as opposed to thiouracil treatment—large unsightly goitres, pressure symptoms, unco-operative patients, under certain circumstances the patient's preference for surgical treatment, and toxic reactions and resistance to thiouracil. Are there any definite indications for thiouracil treatment in preference to surgery?

Undoubtedly thiouracil is the treatment of choice in those rare cases of thyrotoxicosis which occur in children. We have only seen 2 cases under the age of 15 treated with thiouracil and they have both done well. In a child it is difficult to estimate the amount of thyroid tissue to leave when performing thyroidectomy: enough must be left to meet the needs of the growing child, yet insufficient to cause the persistence of thyrotoxicosis. Using thiouracil it is possible to adjust the dose so as to satisfy those requirements. On the opposite extreme it is also better to treat very old thyrotoxic patients with complicating degenerative disease with thiouracil. They are bad surgical risks. Thirdly, patients who develop a recurrent thyrotoxicosis following thyroidectomy should receive medical in preference to further surgical treatment. Fourthly, just as there are patients who have a preference for surgery to prolonged medical treatment and who should be allowed some choice in the matter, so there are others who have a horror of operation and unless there are definite contra-indicating factors they should be allowed *their* preference. To these four groups we personally would add the large group of young women with moderate thyrotoxicosis and unobtrusive goitres who usually seem to react satisfactorily to thiouracil and often seem to be cured by it. The idea of a permanent radical interference with the endocrine system in such cases is repugnant, and, after all, if they do not do well there is always surgery to fall back upon.

We have attempted to indicate the clinical types in which surgery or thiouracil is definitely the treatment of choice. There remains, however, a large number of patients who do not conform to these definite types, and in whom it is best not to adhere to any rigid rule but to treat each patient as an individual problem according to the circumstances of the case.

Lastly, even the opponents of thiouracil treatment grant it a place in the preparation of patients for thyroidectomy. There seems no doubt that following its use the operative mortality—already remarkably low in the hands of experts—has been reduced still further. The method we have adopted is to reduce metabolism to normality by thiouracil, then to stop the drug and to give 0·06 gramme of potassium iodide twice a day for ten to fourteen days prior to operation. By this combined treatment

it is believed that the vascularity and friability of the gland—the only objection to thiouracil as the sole pre-operative treatment—is lessened.

REFERENCE

WILLIAMS, R. H. (1949) *J. Amer. med. Ass.*, **139**, 1064.

Dr. W. R. Trotter: Dr. M. E. Morgans and I have had under observation at University College Hospital upwards of 200 cases of hyperthyroidism, treated solely with antithyroid drugs. Some of these cases have now been watched for periods of up to five years since they finished their initial course of treatment. Our experience has on the whole been so closely similar to that of Professor Dunlop that I shall present data bearing on only one aspect of the problem, namely the liability to relapse after the end of a course of treatment with an antithyroid drug. The data are derived from 110 cases of hyperthyroidism observed for periods of one to thirty-six months after they had finished an initial course of thiouracil or methyl thiouracil (or, in a few instances, thiourea or propyl thiouracil). The average duration of the initial course was slightly over a year. The number of cases naturally decreases with increasing period of observation, only 19 having been observed for the full period of thirty-six months. Because of the varying periods of observation the data have been arranged in the form of a life table, from which the accompanying figure has been constructed. The probability of relapse within any given period after the end of treatment is calculated from the number of patients who have relapsed within that period, and the number of patients at risk during the same period. For this calculation we are indebted to Mr. N. W. Please, of the Statistics Department of University

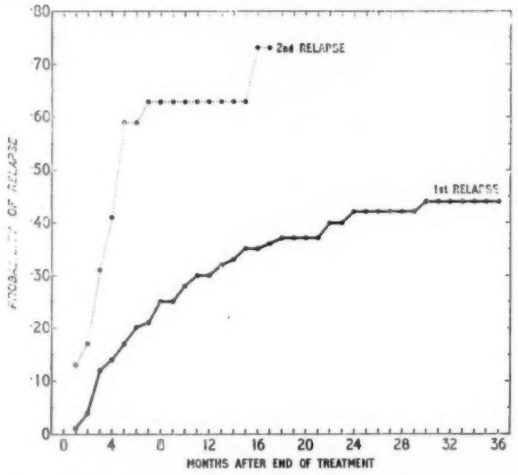


FIG. 1.—The probability of relapse after the end of a course of methyl thiouracil.

College. It appears that the tendency to relapse is greatest in the early months after the end of treatment, and then gradually decreases. From the shape of the curve it seems that not many more relapses are likely to occur after the first thirty-six months. At that time about half the cases have relapsed. Since the number of patients studied gets progressively less the later parts of this curve are less reliable than the earlier, hence deductions from its trend are not perhaps very trustworthy. Nevertheless it seems reasonable to draw the provisional conclusion that when a group of hyperthyroid patients is treated in this way about half will relapse, while the remainder will probably remain well without further treatment for an indefinite period.

23 of the patients who relapsed have been observed after a second course of treatment with an antithyroid drug. The data were treated in the same way and are represented by the dotted line in Fig. 1. It will be seen that the relapse-rate after a second course is decidedly higher than after a single course. From the trend of this second curve it is a fair guess that all cases who have relapsed once will eventually relapse a second time.

If we accept these provisional conclusions, it seems to follow that cases of hyperthyroidism fall into two roughly equal groups: those who have a single, non-recurrent bout of the malady; and those who get repeated attacks. For the first group a course of treatment with an antithyroid drug

is a simple and satisfactory form of treatment; and it scarcely seems justifiable to employ a major operation, or bombardment with radio-active iodine for these brief, isolated bouts of hyperthyroidism.

Those who get repeated attacks of hyperthyroidism can also be treated with antithyroid drugs, and there is no doubt that by careful supervision such patients can be maintained in good health by this means. If no alternative treatment were available this would be regarded as a satisfactory form of therapy comparable to the use of insulin in diabetes, or liver extract in pernicious anæmia. But it becomes somewhat tedious and wearisome to both patient and doctor, and it seems to me that subtotal thyroidectomy is a more appropriate treatment for this relapsing type of case.

It would clearly be advantageous if there were some means of distinguishing these two types of case at the time the patient is first seen. Unfortunately all our attempts to find significant correlations between clinical features and relapse-rate have so far failed, and we are quite unable to predict the likely future behaviour of a hyperthyroid patient at the time we first see him. Another approach would be to find a means of preventing relapses. We are at present trying to see whether relapses can be prevented by the administration of thyroxine, started at the end of the course of thiouracil. Thyroxine, by inhibiting the anterior pituitary, puts the thyroid into a state of inactivity. It will be interesting to see whether the unknown process which causes the relapses is capable of breaking through this artificial hibernation of the thyroid.

But at the moment we have no sure means either of recognizing the cases which are later going to relapse, or of preventing relapses occurring. Under these circumstances I suggest that the most reasonable procedure is to give all cases of hyperthyroidism a course of treatment with methyl thiouracil or a similar drug, lasting about a year. About half the cases will require no further treatment. The remainder will relapse at varying times after they finish treatment, and can then be dealt with by subtotal thyroidectomy, after appropriate preparation.

To this procedure I would make certain exceptions. For three special types of case one or other of the three available methods of treatment seems particularly appropriate. In the first place, all cases in which there is mechanical distortion of the trachea (in addition to hyperthyroidism) are best treated by subtotal thyroidectomy. This group will include most cases of toxic nodular goitre.

Secondly, there are the cases in which hyperthyroidism has recurred after a previous thyroidectomy. A second operation is not desirable, since there is an increased risk to parathyroids and recurrent nerves. Treatment by antithyroid drugs is likely to be tedious since these cases clearly belong to the relapsing group. Radio-active iodine seems the most appropriate treatment for such cases.

Thirdly, there are those cases in which malignant exophthalmos threatens to develop. We know little or nothing about the cause of this condition, except that it tends to become worse if the hyperthyroidism is rapidly removed. By the use of carefully graduated doses of methyl thiouracil the patient can be returned very gradually to a state of normal thyroid function and the threat to the eyes is then minimized.

This scheme may be summarized as follows:

Type of case	*Suggested treatment*
Hyperthyroidism with tracheal distortion	Subtotal thyroidectomy
Hyperthyroidism recurring after previous operation	Radio-iodine
Hyperthyroidism with threatened malignant exophthalmos	Graduated doses of methyl thiouracil
The remainder	A course of methyl thiouracil, followed by subtotal thyroidectomy if relapse occurs

The advantages claimed for this scheme are that it makes use of all three available methods of treatment, and that it avoids a major operation for those patients who can be treated by simpler means. No doubt it will require modification as further experience is gained.

Section of Neurology

President—JULIAN TAYLOR, C.B.E., M.S., F.R.C.S., F.R.A.C.S.

[*May* 4, 1950]

MEETING AT THE MAIDA VALE HOSPITAL FOR NERVOUS DISEASES, LONDON

A Form of Tabes Dorsalis Due to Acute Degeneration of Posterior Root Ganglia.—DOUGLAS MCALPINE, M.D., F.R.C.P., and FRANCIS PAGE, M.D., M.R.C.P.

R. J. K., aged 47, single. Occupation, bar cellarman.

1944: Left side of face suddenly became twisted and left eyelid drooped; no history of diplopia; duration three months. Christmas 1948: Sudden sharp jab of pain in small of back whilst lifting 36-gallon barrel of beer; the pain disappeared after two weeks. Early April 1949: Return of pain in back whilst bending over wash basin; duration two weeks. Late April 1949: Woke up with cold and numb feeling in feet, unable to tell whether he was walking on concrete or sacking and he felt unsteady. He placed his feet against a boiler to get them warm and burned a hole in his sock without feeling pain. Later that day unable to carry his usual two boxes of beer bottles upstairs owing to unsteadiness. Two days later he was accused of being drunk by a policeman; he was quite unaware of his feet touching the ground, and could only walk by looking downwards. The numbness gradually spread up to the groins and walking became more difficult. 1.5.49: Noticed numbness and attacks of momentary sharp pain in the right forearm. No pain in lower limbs. No sphincter disturbance.

4.5.49: Admitted to the Middlesex Hospital.

Examination.—Cheerful, co-operative Irishman. No evidence of recent intellectual deterioration. Pupils moderate size, slightly irregular outline with sluggish reaction to light. Remaining cranial nerves normal.

Motor power: Upper limbs normal. Lower limbs slightly diminished at hip and knee joints.

Reflexes: Deep reflexes present upper limbs; absent lower limbs. Plantar responses flexor.

Tone: Marked hypotonia lower limbs.

Sensation: Loss of all forms of superficial sensation and of deep pain ulnar border of arms and hands, right more than left, on trunk between D2 and D5, and on lower limbs below the knees. Vibration sense diminished in arms; absent in lower limbs up to iliac crests. Postural sense normal in the fingers, but absent in toes, at ankle-joints and knee-joints. Marked ataxia of lower limbs on heel-knee test.

Gait: Grossly ataxic and high stepping on a wide base.

Cardiovascular system: No abnormality. Blood pressure 135/80.

Investigations: Blood W.R. 44441. C.S.F.: Cells 120 lymphocytes per c.mm.; protein 160 mg.%. C.S.F.: Pandy test positive. W.R. 44444. Lange curve 2345553210. Blood count normal. X-ray of chest normal except for slight unfolding of aorta.

Treatment.—Penicillin 7 mega units followed by bismuth and N.A.B.; this treatment repeated at the end of three months. Re-educational walking exercises.

Progress.—During the first few weeks in hospital sensory loss extended to involve the whole body with the exception of a small band round the neck and abdomen; loss of postural sense developed in both hands. Subsequently there was some regression in the extent of sensory loss, and improvement in walking, so that by autumn 1949 he was able to return to light work. 26.8.49: Blood W.R. 44410. C.S.F.: Cells 10 lymphocytes per c.mm.; protein 70 mg.%. W.R. 43100. Lange curve 2343322100. 28.2.50: C.S.F.: Cells 1 lymphocyte; protein 40 mg.%. W.R. 20000. Lange curve 0000000000.

Present condition (26.4.50).—States walking has further improved. Is working as wage clerk. No pain in upper or lower limbs. Feeling in hands has largely returned, but has no feeling in legs or buttocks; cannot feel the chair properly when he sits down or the ground under his feet when walking. Genitalia not affected and has no loss of sexual power. Bladder sensation and control normal. Has gained one stone in weight.

Examination.—Area of sensory loss has diminished, but is still marked, especially for pain on (1) centre of the face, (2) ulnar border of arms and on chest, (3) lower limbs below groins. Still marked loss of postural sense lower limbs, but gait less ataxic.

Dr. Douglas McAlpine: The main feature of this case was the acute onset of ataxia and sensory loss in a syphilitic patient, followed within the next fortnight by a generalized anæsthesia which only spared the neck region, the back of the head and a narrow strip around the abdomen. With the exception of a sharp pain in the right arm at the onset, the patient has not felt pain of any description either before, during the acute phase of the illness or subsequently. Power has remained essentially normal. Thus the clinical picture is similar to that described in 1948 by Denny-Brown under the title "Sensory Neuropathy". This condition occurred in two cases of carcinoma of the lung. In each case there was a spreading and generalized sensory loss on the limbs and trunk with numbness and sensory ataxia; in one of them there was sensory loss on the face. He stressed the fact that neither patient experienced pain, nor was there loss of power. At post-mortem examination the primary lesion in both cases consisted of a severe degeneration of the posterior root ganglia; there was a secondary degeneration of the posterior roots and posterior columns. In addition there was a severe degeneration of the peripheral portion of the sensory neurone. Denny-Brown considered the condition as a unique example of deafferentation in man. By analogy with his cases it seems reasonable to suppose that in this rare example of acute tabes dorsalis there was an acute syphilitic degeneration of the posterior root ganglia as well as of the gasserian ganglion. If this assumption be correct, this case of tabes dorsalis is atypical not only clinically, but also pathologically, since with few exceptions neuropathologists have not considered any changes that may occur in the posterior root ganglia in tabes dorsalis as significant.

A full description of this case, along with other examples of sensory neuropathy of non-malignant origin, will be given in a forthcoming number of the *Archives of the Middlesex Hospital.*

REFERENCE

DENNY-BROWN, D. (1948) *J. Neurol. Neurosurg. Psychiat.*, **11**, 73.

Dr. Helen Dimsdale: This case might be an example of syphilitic polyneuritis, more usually seen in the secondary stage, complicating tabes dorsalis.

Acute Porphyria with Severe Neurological Changes.—L. G. KILOH, M.D., M.R.C.P., and S. NEVIN, M.D., F.R.C.P.

Male, aged 33. In 1924, severe abdominal pain and retention of urine. Laparotomy showed nothing abnormal. Pain persisted, recurring episodically every three weeks for a year. No weakness.

July 1944, following exposure to the sun, patient developed a bullous rash on both upper limbs, which cleared up in three weeks.

October 30, 1949, he complained of severe abdominal pain, distension, constipation and vomiting, with transient diplopia. At laparotomy nothing abnormal was found. Severe pains in the limbs began and he became depressed and delirious at night. Towards the end of November, progressive weakness of all four limbs commenced, he became incontinent of urine and fæces, and he lost much weight. Family history negative.

The patient was seen for the first time on December 20, 1949. Cranial nerves and fundi normal. Weakness profound in arms, less severe in legs, with considerable wasting. Diaphragm paralysed, respiration jerky, cough feeble. Abdominal muscles weak, other trunk muscles normal. Pectoral and biceps jerks just present, other arm reflexes absent. Knee and ankle jerks brisk, plantar reflexes both extensor. Moderate impairment of superficial sensation over lower trunk and thighs. All muscles tender.

Mental state: Retarded, a little confused and depressed. Blood pressure 135/85.

Investigations.—C.S.F. : Protein 130 mg.%, otherwise normal.

Electrical reactions and electromyography: Severe partial reaction of degeneration. Many denervation potentials.

E.C.G.: Right bundle branch block.

E.E.G.: Abnormal, showing dominant post-central rhythm of 6 c/sec. with paroxysms of widespread 2 c/sec. activity (Fig. 1).

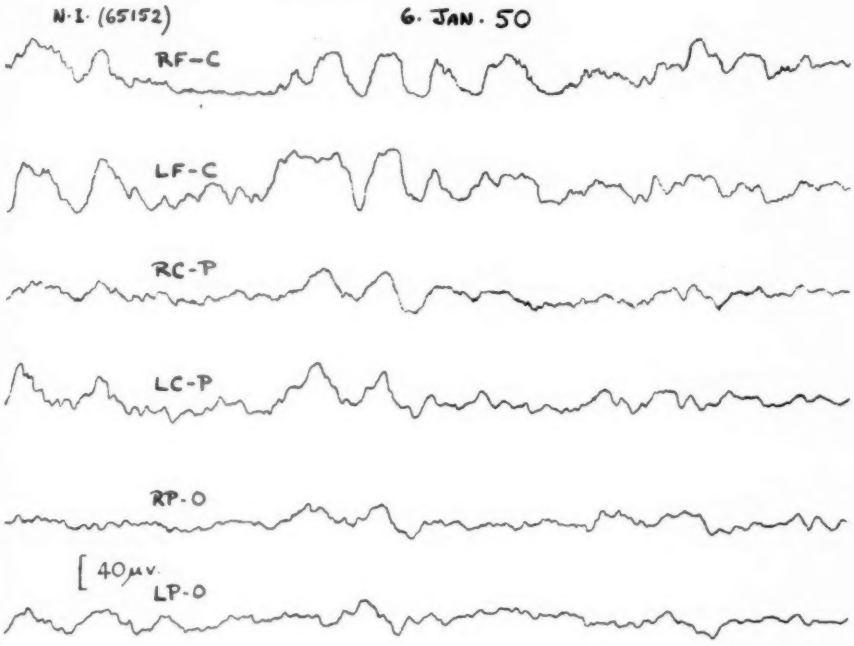


FIG. 1.—E.E.G., 6.1.50. Dominant post-central rhythm of 6 c/sec. with widespread paroxysms of 2 c/sec. activity.

By 16.3.50 the E.E.G. was normal. (The E.E.G. reports are published through the courtesy of Dr. Denis Hill.)

Urine and fæces: Urine contained uroporphyrin III and coproporphyrins I and III. Coproporphyrins I and III isolated from fæces in relatively large amounts. (These results are quoted through the courtesy of Professor C. H. Gray.)

The weakness, pain in abdomen and limbs, persisted until early March 1950, but the incontinence and mental changes improved and porphyrins disappeared from the urine. Power then began to return rapidly in the limbs and diaphragm, in spite of the fact that excretion of porphyrins recommenced. By mid-April, could walk and feed himself. The signs of pyramidal tract disturbance persisted.

POSTSCRIPT (December 1950).—Discharged from hospital 25.5.50. Except for severe bilateral wrist drop, power everywhere almost normal. Improvement subsequently continued and extensors of the wrist showed considerable recovery. On 1.11.50 severe abdominal pain recurred and has persisted.

Readmitted to hospital 10.11.50. Pain has since commenced in all four limbs, but as yet no paralysis has appeared. He is constipated and has retention of urine. Apart from mild confusion for three days, he has had no mental symptoms. Signs of pyramidal tract damage have become more obvious as his muscular power has improved. Since admission his urine has gradually deepened in colour and now contains larger quantities of porphyrins than ever before.—L. G. K.

Poliomyelitis with Sensory Signs.—P. H. SANDIFER, F.R.C.P.

Male, aged 30, admitted under Mr. H. J. Seddon (by whose courtesy this case is reported) at the Royal National Orthopædic Hospital, Stanmore, on 7.3.50.

1.11.49: His 2-year old son developed poliomyelitis, and was treated at the Hospital for Sick Children; he has completely recovered save for paresis of left hand.

3.11.49: Patient himself developed painful stiff neck, later nausea and vomiting; he took to his bed.

5.11.49: Weakness of the arms; next day, admitted to Royal Free Hospital with gross paralysis of both arms. He developed diplopia which lasted three weeks.

Lumbar puncture.—Pressure 190 mm.; C.S.F.: Protein 120 mg.%. Cells 177 per c.mm., 94% lymphocytes.

10.11.49: Overnight, complete flaccid paralysis of both legs, retention of urine, loss of rectal control and complete sensory loss up to groins in front and buttocks behind.

5.12.49: Second lumbar puncture: slightly xanthochromic fluid; protein 450 mg.%. Cells 12 per c.mm. (lymphocytes). C.S.F. sterile; W.R. and Kahn negative. No spinal block.

Subsequent progress.—Urethral sensation and awareness of bladder distension began to return in February 1950; precipitate reflex micturition developed in March, and tidal drainage was discontinued altogether in April, and there has been efficient reflex micturition since; he is able to initiate but not prevent micturition by voluntary effort. Rectal and anal sensation began to return in January, when he developed precipitate defæcation; he now has efficient reflex defæcation. Cutaneous sensory loss began to recede from the groins in January, and to diminish in intensity elsewhere; he now shows blunting of skin sensation in the dermatomes L.5–S.5, which is minimal over both calves.

Joint sense is absent from the toes, and vibration sense reduced in the legs. Moderate motor recovery has occurred at the right shoulder girdle, and a little in the left forearm and hand, but on the right side there remains gross paralysis of the elbow extensors and forearm and hand muscles, whilst on the left side the paralysis is less than on the right. In the legs, there is complete flaccid paralysis. All his tendon-jerks are lost, and the plantar responses are abolished.

Comment.—The identity of the virus producing this illness has never been proved. But there are not less than two pieces of evidence which support the view that it was a poliomyelitis virus. There is the fact that his son developed what was clinically typical poliomyelitis shortly before this illness developed. Then there is the fact that the evolution of the early stages of this illness was typically poliomyelitis—up to the time, indeed, when a complication of some kind developed—a complication one might call "transverse myelitis".

The mechanism of this complication has never been proved. There is no post-mortem or biopsy material. But, I think, the behaviour of his C.S.F. affords a clue. After this complication the C.S.F. proteins rose from 120 to 450 mg.%. The fluid became xanthochromic, but there was no block. To me this suggests a vascular pathology—that the inflammatory reaction and vascular changes in the lower part of the cord were excessive—so excessive, indeed, that hæmorrhage and thrombosis were on a scale large enough to deprive several segments of the cord of their blood supply.

Dr. Douglas McAlpine: This is an unusual example of a rare form of poliomyelitis. I have seen about half a dozen cases of acute myelitis occurring in this condition. When the cervical enlargement is hit there is not much difficulty about the diagnosis since there is a combination of lower and upper motor neurone signs with sensory loss. However, in a dorsal myelitis due to poliomyelitis virus, difficulties in diagnosis may be considerable. Should constitutional symptoms and meningeal signs be prominent, and should poliomyelitis exist in the neighbourhood, the diagnosis should not be difficult. In other cases reliance must be placed on the changes in the C.S.F. I do not think it is necessary, as Dr. Sandifer has suggested, to postulate a vascular lesion in order to account for the changes in the C.S.F., in his case. A high protein content in the third or fourth week is not unusual.

Late Hereditary Distal Myopathy.—J. B. STANTON, M.B., M.R.C.P., for W. RUSSELL BRAIN, P.R.C.P.

W. G., aged 55. Excavator driver.

10 years ago: First noticed that his legs felt cold and "dead" and began to have difficulty in walking. At this time, and for the following two years, he had severe cramps in the legs at night.

Seven to eight years ago: His hands became weak and wasted, and when seen in Outpatients he was found to have also extensor plantar responses; he was diagnosed as having

amyotrophic lateral sclerosis; the weakness of the hands and difficulty in walking have increased, so that he took to riding a bicycle, and has walked less and less.

No sphincter disturbance. No loss of weight. Right-handed.

Past history.—1916: Trench foot. 1919: Accidental fracture of right mandible, repaired by graft.

Family history.—His parents were first cousins. One elder sister has recently developed a "neuromuscular disorder", while living in New York, and cannot walk now.

On examination.—Looks in good health. Gait shuffling and very unsteady. Spine: Right dorsal and left lumbar scoliosis. Fundi and other cranial nerves normal, except old deafness on right.

Motor system.—Marked wasting and weakness of small muscles of hands and of forearms, left more than right. Fasciculation seen in triceps and biceps. Wasting of legs, left more than right, with flail ankles and weakness of all leg muscles most marked distally. Weakness of recti abdominis. Co-ordination normal in arms and legs.

Sensation.—Peripheral diminution to pin-prick and light touch in hands and legs. Joint sense, vibration sense normal.

Reflexes.—Arm-jerks all very sluggish. Abdominal reflexes absent. Knee and ankle jerks absent on reinforcement. Plantar responses extensor R. and L.

Skin dry and scaling over legs and feet.

Other systems normal.

C.S.F.: Pressure 40 mm. Protein 20 mg.%. Cells nil.

POSTSCRIPT (December 1950).—Since this case was shown Dr. Brain has drawn attention to the paper by Welander (1946) describing a late hereditary distal myopathy having the following characteristics: late onset (30–50 years of age), heredofamilial incidence, protracted course and distal distribution in arms and legs. It is thought that the case presented above resembles this group more closely than it does other types of muscular atrophy.—J. B. S.

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Spinocerebellar Degeneration.—MICHAEL ASHBY, M.R.C.P.

G. E., male aged 56.

1945: Onset of dragging of the right leg, very gradually progressive. Fell down occasionally, right arm became ataxic about two years later.

December 1948: Severe exacerbation of ataxia overnight. Had been to work the day before, but next morning he could only stand but could not walk.

July 1949: Gradually becoming worse, got steadily more ataxic. Attended Out-patients at the National Hospital.

November 1949: Admitted under Dr. Denis Brinton. Low intelligence noted. Signs materially as now, including extensor plantar responses.

Ataxia has further progressed. Mental state was erratic, being exceptionally alert but gauche and childlike in manner.

On examination.—Gross myopia with crescents. Blood pressure 140/95. Discs not abnormally pale. Variable nystagmus, occasionally vertical as well. Complete right VI nerve paresis. Palate shows slight right weakness. Slight dysarthria.

Motor system.—No weakness, and not spastic when he can be persuaded to relax. Gross cerebellar ataxia of legs and trunk, less severe of upper limbs.

Sensation.—Postural sense impaired in his toes but vibration, deep pain and other modalities preserved.

Reflexes.—Brisk and equal tendon-jerks. Abdominal reflexes very sluggish. Bilateral extensor plantar responses.

X-rays of skull and chest show no evidence of neoplasm.

Lumbar puncture.—Pressure 80 mm. C.S.F. normal in all respects; 2 cells per c.mm. W.R. negative in blood and C.S.F.

Diagnosis.—Clearly a degenerative disorder in view of the steady progression in the absence of any evidence of neoplasm.

Although atypical, especially with regard to the rectus palsy and only slight dysarthria, this picture most closely resembles olivo-ponto-cerebellar atrophy.

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Section of Medicine

President—Sir ADOLPHE ABRAHAMS, O.B.E., M.A., M.D., F.R.C.P.

[*May* 23, 1950]

DISCUSSION ON THE PATHOGENESIS AND TREATMENT OF THE MEGALOBLASTIC ANÆMIAS

Dr. R. Bodley Scott: The megaloblastic anæmias—a term we owe to Professor Davidson—are those in which the bone-marrow shows the characteristic perversion of megaloblastic hyperplasia. This is not always so clear cut as in the classical pernicious anæmia, but is sometimes combined with normoblastic proliferation to give a mixed or, what Trowell (1943) has called, a "dimorphic" picture. An occasional megaloblast-like cell, such as is seen in leuko-erythroblastic anæmia and di Guglielmo's disease, does not qualify an anæmia for inclusion in this group. Defined in this fashion, the following varieties of megaloblastic anæmia may be recognized (Table I).

TABLE I.—THE MEGALOBLASTIC ANÆMIAS

1. Addisonian pernicious anæmia
2. Pernicious anæmia of *D. latum* infestation
3. Megaloblastic anæmia of total gastrectomy and other gastric operations
4. Nutritional (tropical) megaloblastic anæmia
5. Megaloblastic anæmia of sprue and other steatorrhœas
6. Megaloblastic anæmia of intestinal stricture and resection
7. Megaloblastic anæmia of pregnancy and the puerperium
8. Megaloblastic anæmia of infants
9. Achrestic anæmia

In these anæmias the logical order has been reversed, for each accretion to our knowledge of their cause has sprung from a therapeutic advance; the process began in 1926 when Minot and Murphy showed that patients with pernicious anæmia recovered if given a diet containing half a pound of liver a day. The original impetus had been provided by Whipple and Robscheit-Robbins' demonstration (1925) that liver had a peculiar efficacy in causing regeneration of hæmoglobin in the experimental post-hæmorrhagic anæmia of dogs. The non sequitur, later apparent in Minot and Murphy's reasoning, in no way detracts from the far-reaching importance of their discovery. Their observations changed the course of hæmatology, replacing the sterile contemplation of cellular detail by a dynamic approach to the problems of ætiology. Within four years Castle (1929*a*, *b*) had shown that a mixture of beef protein and normal gastric juice, given orally, would induce remission in pernicious anæmia, while alone neither was effective. On these facts, which have been confirmed many times, was built the hypothesis generally accepted until a few years ago.

Castle suggested that two principles were essential for healthy blood formation: one, the extrinsic factor, was normally present in the diet; the other, the intrinsic factor, was secreted by the gastric mucosa. An interaction between these two took place in the alimentary tract and its product, the liver principle, was absorbed from the bowel and stored in the liver. The several megaloblastic anæmias could all be explained on this basis: in Addisonian pernicious anæmia, gastric secretory failure was responsible for deficiency of intrinsic factor; in nutritional megaloblastic anæmia, the diet was lacking in extrinsic factor; defective absorption from the alimentary tract would account for most of the remainder.

In the next few years the nature of these factors was the subject of energetic inquiry. *Intrinsic factor* was found to be secreted by the gastric mucosa of most carnivora, but not herbivora. The site of its secretion was proved to vary with the species: in the pig it was the pyloric region, in man the fundus and cardia. The factor was thermolabile, being rapidly inactivated by a temperature of 60° C. Wilkinson (1949), to whom we owe much of our knowledge of this substance which he has called "hæmopoietin", found that when concentrates were incubated with beef protein the resulting product was actively hæmopoietic after prolonged heating to 60° C. It was concluded that the intrinsic factor was an enzyme, most active within the pH range 7·4–7·7 (Taylor *et al.*, 1938). Its relation to apoerythein is discussed later.

Extrinsic factor activity was found in a wide range of substances including beef muscle, milk, eggs, rice polishings, yeast, wheat germ, and liver. It was thought to be an unidentified thermostable component of the vitamin-B complex (Castle *et al.*, 1944).

The first blow to Castle's unitarian hypothesis was the demonstration by Wills in 1938 that, in her patients with nutritional megaloblastic anæmia, Marmite would induce remission while refined liver extract, known to be potent in pernicious anæmia, was ineffective. This could only mean that some factor, other than the liver prineiple, was required. During the next few years it became apparent that several varieties of megaloblastic anæmia responded

poorly, or not at all, to refined liver extract of proven potency in pernicious anæmia. These Davidson (1948) termed "refractory" and he, amongst others, showed that many of them recovered when treated with proteolysed or whole liver by mouth. These observations again were impossible to explain without postulating an additional factor.

In 1946, Angier and others synthesized folic or pteroylglutamic acid. The story of this substance has often been told (Welch, 1947; Wilkinson, 1948): *Lactobacillus casei* and *Streptococcus lactis R* had both been found to need for their growth a factor present in yeast, liver extract, and spinach leaves. This had come to be known as folic acid. It later became clear that many "folic acids" existed, some of which were equipotent for both organisms, while others were active only for *Str. lactis R* unless first subjected to enzymic digestion. Angier's work showed that the essential growth-promoting substance was the crystalline *L. casei* factor of liver, which he proved to be pteroylglutamic acid and was later able to synthesize. Other, naturally occurring, folic acids were conjugates of pteroylglutamic acid with varying numbers of molecules of glutamic acid. These conjugates only acquired full growth-promoting activity when broken down to the parent substance by enzymes spoken of as conjugases.

Pteroylglutamic acid was soon shown to be identical with the factors, previously known as Vitamins B_c and M, curative of nutritional macrocytic anæmia respectively in chicks and monkeys (Pfiffner *et al.*, 1943 ; Wilson, Saslaw and Doan, 1946). It was but a short step to employ this substance in human megaloblastic anæmia, and there have been many reports of its action in the past four years. It will correct the megaloblastic hyperplasia of the bone-marrow in all the anæmias of this group. It will not, however, prevent the onset of neural degeneration in pernicious anæmia, in fact it often seems to occasion its explosive appearance. Its use has even been followed by this complication in other megaloblastic anæmias in which disease of the nervous system is usually of great rarity (Meyer, 1948). Nervous degeneration does not occur when it is given concurrently with liver extract, nor is it seen when pteroylglutamic acid is given to patients with hypochromic anæmia for periods as long as two years (Harvey, Howard and Murphy, 1950). It will not control the glossitis of pernicious anæmia and, after a period, it may fail to maintain normal blood levels in patients with this disease. Occasional examples of pernicious anæmia have proved refractory to pteroylglutamic acid (Hansen-Pruss, 1947; Mollin, 1948).

These observations led to the hypothesis that pteroylglutamic acid was the ultimate principle essential for the preservation of normoblastic erythropoiesis (Davidson, 1949). It was clearly not the extrinsic factor, for it was active orally in the absence of gastric juice; it was not the liver principle itself because, even before the isolation of vitamin B_{12}, it had been shown that liver extracts, virtually free of pteroylglutamic acid, were active in pernicious anæmia. It was postulated that a defect of conjugase activity was the underlying fault. The diet normally contains a mixture of conjugates, but no free pteroylglutamic acid. The patient with pernicious anæmia, it was suggested, had lost the power to deconjugate these substances and was thus deprived of pteroylglutamic acid in an available form. Liver extract, it was thought, increased conjugase activity and brought about the liberation of normal amounts of free pteroylglutamic acid.

Experiments to prove this contention have been unsatisfactory. Although full remission has been recorded after injection of large doses (Wilkinson and Israëls, 1949), in general it is true that the response of pernicious anæmia to oral or parenteral administration of conjugates is less satisfactory than to an equivalent amount of pteroylglutamic acid. However, the same is true of the other megaloblastic anæmias. There is no evidence that liver extract stimulates conjugase activity and this hypothesis can no longer be seriously entertained.

The observation that thymine could replace pteroylglutamic acid as a bacterial growth factor led to its use in megaloblastic anæmia (Spies *et al.*, 1946); in doses of 6–10 grammes daily it has been shown to procure remission, although, like pteroylglutamic acid, it will not control glossitis or neural change. It has been suggested that pteroylglutamic acid is an enzyme concerned in the synthesis of thymine or related compounds.

Since the publication of Minot and Murphy's paper in 1926, continuous attempts to isolate and identify the substances in liver, possessing anti-anæmic properties, have been in progress. Success was achieved in April 1948 when a team working at Merck's Laboratories in the United States (Rickes, Brink, Koniuszy, Wood and Folkers, 1948*a*) and Lester Smith of Glaxo Laboratories in this country (1948*a*) published, within a week of each other, reports that they had isolated a red crystalline pigment from liver, actively hæmopoietic in minute doses. This substance, now known as vitamin B_{12}, has been shown to have a molecular weight of about 1,500 and to contain one atom of cobalt and one of phosphorus (Smith, 1948*b*, 1949; Rickes *et al.*, 1948*b*).

For their isolation the American group made use of a growth-factor method. Shorb (1947) had found that the growth requirements of *L. lactis* Dorner included a factor in liver extract, and that the concentration required bore a linear relationship to the anti-anæmic

potency of the extract in question. Her suggestion that the unknown factor was the liver principle itself provided the Merck team with a simple means of assay. Lester Smith employed the more tedious methods of partition chromatography and clinical trial of each fraction. His chromatographic analysis of liver extract has yielded, as well as vitamin B_{12}, two other red pigments effective in pernicious anæmia. One of these, vitamin B_{12b}, has been isolated in crystalline form (Pierce, Page, Stokstad and Jukes, 1949); the label B_{12a} has been reserved for an artificial hydrogenation product of vitamin B_{12} (Kaczka, Wolf and Folkers, 1949).

Vitamin B_{12} has proved fully effective in pernicious anæmia; its administration is followed by repair of anæmia, healing of mucosal lesions, and arrest or improvement of the neural degeneration. The results in other forms of megaloblastic anæmia are less clear cut.

Evidence has accumulated that substances with a vitamin B_{12} activity are as widely distributed in nature as the folic acids. Various growth factors for chicks and rats, known as factor X, cow-dung factor, animal protein factor, and zoopherin can all be replaced by vitamin B_{12} (Ott, Rickes and Wood, 1948; Nichol, Dietrich, Cravens and Elvehjem, 1949); and some of these substances have proved to have hæmopoietic activity (Spies *et al.*, 1949). A red pigment is elaborated during the growth of *Streptomyces griseus* in fluid media; this has been isolated in crystalline form and appears to have all the properties, and to be identical with vitamin B_{12} derived from liver (Rickes *et al.*, 1948*c*). This product is now marketed and has proved fully effective in the treatment of pernicious anæmia. *Streptomyces aureofaciens* produces a like substance with vitamin B_{12} activity in the same dosage as that of *griseus*, but with a different absorption spectrum (Lichtman *et al.*, 1949). It is uncertain whether these are conjugates of vitamin B_{12} or closely related chemical modifications of it.

Vitamin B_{12}, even in massive doses, is ineffective when given by mouth to patients with pernicious anæmia unless accompanied by normal gastric juice (Berk *et al.*, 1948; Hall, Morgan and Campbell, 1949). The simultaneous administration of 5 μg and 50 ml. of normal gastric juice has a hæmopoietic effect equivalent to about 10 μg of the vitamin given parenterally (Ungley, 1950). Extract of hog's stomach or duodenum, itself without anti-anæmic activity, can effectively replace human gastric juice in this experiment (Hall *et al.*, 1950). On these grounds, it seems probable that the functions of vitamin B_{12} are those of Castle's extrinsic factor. The role of the intrinsic factor appears to be the potentiation of the vitamin's absorption from the alimentary tract (Bethell *et al.*, 1949). There is some evidence that an actual combination of the two factors takes place, for a mixture of gastric juice and vitamin B_{12} is more heat-stable than the factor in gastric juice alone (Hall *et al.*, 1950). A substance has recently been isolated from human gastric juice which combined quantitatively with vitamin B_{12}, depriving it of its ability to promote bacterial growth. This product, which has been named "apoerythein", resembles, in its physical properties, Castle's intrinsic factor and Wilkinson's hæmopoietin (Ternberg and Eakin, 1949).

The probability of bacterial synthesis of vitamin B_{12} in the lower reaches of the alimentary tract in man and animals has been demonstrated (Dyke, Hind, Riding and Shaw, 1950). It is uncertain whether this is the method by which normal requirements are met or whether it is another instance of the prodigality of Nature.

The mode of action of vitamin B_{12} is unknown. Its relation to thymidine, or thymine desoxyriboside, presents a parallel to that of pteroylglutamic acid and thymine. Thymidine can replace the vitamin as a growth factor for many, but not all, bacteria (Shive, Ravel and Eakin, 1948). It has been suggested that vitamin B_{12} is an enzyme concerned in the conversion of thymine to thymidine (Wright, Skeggs and Huff, 1948). However, there is no evidence that thymidine plays a part in hæmopoiesis; in doses up to 150 mg. it has not procured remission in pernicious anæmia (Ungley, 1949; Reisner and West, 1949; Ten Berg *et al.*, 1949).

Factual knowledge has accumulated so rapidly in the last five years that understanding has been left far behind. The difficulty of weaving these facts into a plausible successor to Castle's hypothesis is obvious. A little help is given by tabulating the effects of vitamin B_{12} and pteroylglutamic acid in the various megaloblastic anæmias (*see* Table II). The table shows that Addisonian pernicious anæmia differs from most of the other members of the group in being completely relieved by vitamin B_{12} and refined liver extract, while pteroylglutamic acid confers but variable and partial benefit. It is reasonable to class the megaloblastic anæmia of total gastrectomy with it, and there is evidence that the presence of the broad tapeworm impedes the interaction of Castle's two factors in the alimentary tract (von Bonsdorff, 1948). In these three, therefore, there is a disturbance of the intrinsic-extrinsic factor mechanism. Revising our vocabulary by substituting vitamin B_{12} for extrinsic, and apoerythein for intrinsic, factor, the stubborn facts of Castle's original experiment can be made to explain the conditioned deficiency of vitamin B_{12} in these three anæmias.

In the remainder, pteroylglutamic acid is usually fully effective and the action of vitamin B_{12} variable; there is no proven disturbance of the intrinsic-extrinsic factor machinery. The relationship between these two categories of megaloblastic anæmia, if in fact one exists, has yet to be elucidated. In many instances some effect is obtained with either drug;

TABLE II.—ACTION OF VITAMIN B_{12} AND PTEROYLGLUTAMIC ACID IN THE MEGALOBLASTIC ANÆMIAS

	Vitamin B_{12} and liver extract by injection	Pteroylglutamic acid
1. Addisonian pernicious anæmia	Completely effective	Variable effect on anæmia; none on C.N.S. or tongue
2. Pernicious tapeworm anæmia	Effective	Effective
3. Megaloblastic anæmia of total gastrectomy ..	Effective	Effective
4. Nutritional megaloblastic anæmia	Variable	Effective
5. Megaloblastic anæmia of steatorrhœa ..	Variable; some refractory	Effective
6. Megaloblastic anæmia of intestinal stricture	Variable; some refractory	Effective
7. Megaloblastic anæmia of pregnancy ..	Ineffective	Effective
8. Megaloblastic anæmia of infants	Variable	Effective
9. Achrestic anæmia	Ineffective	Effective

occasionally both may be required; perhaps the truth lies in Welch's suggestion (1947) that the metamorphosis of raw material into the substances essential for normal hæmopoiesis follows two alternative pathways, neither of which is alone entirely adequate; along one of these routes pteroylglutamic acid acts as a catalyst, along the other vitamin B_{12}. Although there are indications that changes in the bacterial flora of the bowel may be of importance, it is not yet clear how deficiency of pteroylglutamic acid arises.

For the moment the therapeutic implications seem definite: in pernicious anæmia treatment should be with vitamin B_{12} or liver extract; in the second group the indication is for pteroylglutamic acid.

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Dr. G. M. Watson (The Nuffield Department of Clinical Medicine, Oxford): It is interesting to see how two main theories on the pathogenesis of the megaloblastic anæmias have held the field, supplanting one another in turn; recent work suggests that we may still derive something from both the theories.

The earliest observers (Fenwick, 1870) noticed the gastric atrophy and lack of gastric secretion present in pernicious anæmia and made the natural assumption that the disease arose from an inadequate absorption of food, a view not very different from that which most people hold to-day. Within a few years, however, some evidence of hæmolysis was noticed in the disease, and this did not appear to be compatible with the earlier theory. It was well known then, though often overlooked now, that gastro-intestinal symptoms are common in pernicious anæmia. This gave rise to the toxic and hæmolytic theory of the disease for it was thought that achlorhydria predisposed the patient to infection of the small intestine and that the pathological phenomena of pernicious anæmia were due to toxins formed by intestinal organisms. When no specific treatment was available fluctuations and remissions in the course of the disease were commonly observed, and these could easily be accounted for by the vagaries of the population of intestinal bacteria. This theory is worth particular notice for, in a sense, it has recently been brought forward again, though now the bacteria are postulated as acting in a very different way.

The discovery of liver treatment brought back the older view. It was an obvious assumption that some factor in liver was necessary to normal hæmatopoiesis, and that this factor was lacking in patients with pernicious anæmia. Castle's remarkable series of observations seemed to show how this deficiency came about and had the advantage that megaloblastic anæmias other than pernicious anæmia could be explained by assuming interruptions at various points in the chain of events leading to the utilization of the anti-anæmic principle.

The facts of Castle's experiments have never been in doubt, and indeed have recently received fresh confirmation by recent work on the potentiation of vitamin B_{12} by gastric juice, but their interpretation gradually became less clear than seemed at first apparent. The idea of pernicious anæmia as simply a deficiency disease tended to overlook some of its features such as its remittent character and the evidence of hæmolysis. Moreover the failure of animal experiments based on Castle's hypothesis was not easily explained. On this hypothesis experimental resection of the stomach should have produced pernicious anæmia. This was a reasonable assumption as it has been shown that livers from a wide range of animal species contain the anti-anæmic principle. The failure could not be explained by assuming that intrinsic factor was formed elsewhere than in the stomach, for very extensive gastro-intestinal resections were equally unsuccessful. Similarly it should have been possible to produce pernicious anæmia by withholding extrinsic factor from the diet, but experiments of this kind were generally unconvincing. It was not until some recent work with pigs (Heinle *et al.*, 1947; Cartwright *et al.*, 1949) that a macrocytic anæmia has been produced in experimental animals with any regularity by dietary means, and then not merely with a synthetic diet but by adding to it sulphonamide and a folic acid antagonist, and this can hardly bear a close relation to any natural disease. Because of these discrepancies there was, in some quarters, a revival of interest in the older toxic theory.

The next great advance was the isolation of folic acid and the demonstration of its remarkable range of action in the megaloblastic anæmias. It was soon apparent that folic acid was not the long-sought liver principle but it did seem possible that it might be the final agent by which liver acted on the bone-marrow. It was at first thought that liver principle might liberate free folic acid from the conjugated forms in which it is mostly present in food and permit its absorption or utilization, but this attractive theory has not withstood

close examination and is not now widely accepted. It has been shown that persons with pernicious anæmia are as well able as normal subjects to utilize conjugated folic acids, provided that the conjugated acids are not accompanied by an excess of the naturally occurring inhibitors of the splitting reaction.

This brief review of theories on the pathogenesis of the megaloblastic anæmias is almost up to date, for, in the last year or so, new observations seem to have outrun the powers of theoreticians on this subject. The isolation of the pure hæmatopoietic principle from liver, now called vitamin B_{12}, is of great interest but the mere fact of its discovery has not really advanced knowledge of the basic processes by which the megaloblastic anæmias are produced. It is now necessary to consider what are these basic processes, and what evidence there is, old or new, which may help to elucidate them.

The Nature of the Problem

There is a group of diseases—true pernicious anæmia, the pernicious anæmia of pregnancy, nutritional macrocytic anæmia, the steatorrhœas, fish tapeworm anæmia and the macrocytic anæmia occasionally associated with gross surgical disease of the intestine—in which, though there are many points of difference, yet the appearance of the bone-marrow may be the same in them all. It will not do simply to say that they are different diseases; so they are, but it is necessary to know for each one the mechanism by which a megaloblastic bone-marrow reaction is produced, and any hypothesis on the pathogenesis of the megaloblastic anæmias should be capable of extension to cover all of them. It may be helpful to break the problem down into two parts; firstly what may be called the metabolic lesion directly responsible for the megaloblastic reaction in the marrow, and secondly the pathological changes, whether they be anatomical, physiological, bacteriological or even dietary, which provide the conditions for the metabolic lesion.

The Metabolic Lesion

It is in relation to what, for want of a better term, the present writer has called the metabolic lesion that one might expect to find similarities between the several diseases already mentioned but at the outset there is the puzzling fact that they have differing responses to vitamin B_{12}. There is evidence on this aspect of the problem from several different sources. Firstly there are the different therapeutic actions of folic acid and vitamin B_{12}. In view of the wide range of action of folic acid it is tempting to suppose that its action is at a later stage than that of vitamin B_{12}, and may well be directly on the marrow cells. The fact that vitamin B_{12} will prevent nervous lesions whereas it seems that folic acid will not, also points to an earlier action of vitamin B_{12}. Another pointer to a wider action of vitamin B_{12} is that it has been found to be a growth factor for the young of several species, and we know it to benefit glossitis.

Secondly some indirect evidence has been provided on the actions of folic acid and vitamin B_{12} by microbiological experiments in which these two substances are replaceable by thymine and thymidine respectively. Thymine, in large doses, has been shown to be effective in some macrocytic anæmias, and the same has been claimed for thymidine by one author (Hausmann, 1949), though others have had negative results. Finally an obvious way to study the action of hæmatopoietic substances is to determine their effects on cultures of marrow cells, the technical difficulties involved in this method have prevented its extensive use, but in 1948 a group of workers (Rusznyák, *et al.*, 1948) reported that while folic acid had a maturing effect on erythroblasts in culture, serum from patients with pernicious anæmia had an inhibiting effect. Lajtha (1950) has since reported that vitamin B_{12} does not have the same effect as folic acid, and that serum from patients with pernicious anæmia will produce megaloblasts from normal marrow cells.

There is evidently, as yet, insufficient information from which to deduce just what is happening in the marrow. Hypotheses have been constructed which relate folic acid and vitamin B_{12} to the synthesis of nucleic acids but they are still speculative and do not fit overwell with the observed clinical facts of the disease. On the other hand if the observations on marrow cultures can be confirmed they will be difficult to explain on the assumption that pernicious anæmia is simply a deficiency disease. They are reminiscent of the theory put forward before the war that liver extract might act by neutralizing or preventing the absorption of some toxic agent formed in the bowel. It is improbable that we can discount folic acid from consideration, as some recent writers have done, for it is not unlikely that, if pernicious anæmia is a deficiency disease at all, it is ultimately a deficiency of folic acid.

The Pathological Lesions

It is in relation to the grosser lesions permitting the histological end-result which can be recognized as megaloblastosis that we have been most guilty, both of neglecting the older observations and of insufficiently studying the diseases themselves. To consider further this aspect of the problem it will be simplest to state a hypothesis and then endeavour to justify and expand it. It is not the present writer's belief that the development of pernicious

anæmia is conditioned solely by the loss of the specific gastric secretion that we know as the intrinsic factor. If this is so some other conditioning agency must be sought which, after preliminary loss of the intrinsic factor, brings about the disease. It is suggested that we must look for this second change in the small intestine, and there is some evidence that this change may be bacteriological. This being so the mode of action may simply be a toxic process, as in the old view, or it may be in accord with the modern idea that the intestinal bacteria may compete with the host for essential food substances. It may be that both play a part.

It was said earlier that the loss of the intrinsic factor may not be the only element determining the onset of pernicious anæmia and there is some evidence for this statement. The results of animal experiments designed to produce pernicious anæmia by gastrectomy cannot be disregarded. Of course one cannot always argue from animal experiments to the human case but there is confirmation of this view from the results of human gastrectomy, after which pernicious anæmia by no means invariably follows, and is always considerably delayed. We know also that it is possible to have a megaloblastic anæmia despite the presence of intrinsic factor in the gastric juice. This has been shown to be the case in occasional examples of the various megaloblastic diseases other than pernicious anæmia. The rather facile explanations which have been advanced to explain this, such as interference with the combination of intrinsic and extrinsic factors or with absorption of their product, are not very convincing. In view of all this it is surprising that there appears to be no extensive enquiry on this point. It is true that Castle did report that intrinsic factor was present in the gastric juice of 4 patients with achlorhydria and without pernicious anæmia but no extensive investigation has been made. Certainly Barnett (1932) reported that intrinsic factor was lacking in the gastric juice of 2 patients with achlorhydria who did not have pernicious anæmia, and three years later they still had not developed the disease (Bloomfield and Pollard, 1935). There is a case for more investigation on this point; it would be of interest to examine and follow up the relations of persons with pernicious anæmia.

A Further Factor in the Pathogenesis

If it is possible for a subject to have a deficiency of intrinsic factor, for a time at least, without necessarily developing pernicious anæmia, we must look for a further factor in the ætiology of the disease. One way of doing this is to look more closely at the several diseases in which a megaloblastic marrow may be a feature and try to find a common factor between them. There are many points of difference but there is at least one point in common. In all of them there is usually some evidence of intestinal disorder. This may be conspicuous, as in the steatorrhœas, or relatively inconspicuous as in pernicious anæmia or nutritional macrocytic anæmia, but it is commonly there. Other than this these diseases have remarkably little in common. It is not simply a question of steatorrhœa although this may be present in several of these diseases, for patients with pernicious anæmia have been shown not to have steatorrhœa, and it may be present or absent in some of the others. In the absence of any characteristic pathological finding it is tempting to wonder whether the hypothetical change can be related to the bacterial flora of the bowel, as used to be thought by the advocates of the toxic hæmolytic theory, and, in fact, recent work has again drawn our attention to the flora of the bowel.

Other than by dietary means macrocytic anæmia has been produced in animals only by forming strictures or diverticula in the small intestine, or by forming a gastro-colic fistula. All these procedures are accompanied by infection of the small intestine; its normally scanty flora become abundant and of the type usually associated with the colon. Frazer (1949) has discussed the question of intestinal infection in relation to the vitamin deficiencies and hæmatological changes of sprue. He and his colleagues have shown that in sprue there is heavy infection of the small intestine with organisms of the colon, the infection being greatest when achlorhydria is present. They suggest that the B-vitamin deficiencies present in sprue arise from competition with the host by the abnormal flora. There is evidence to show that intestinal bacteria require and, if necessary, synthesize most of these vitamins. Ordinarily these organisms are confined to the large bowel and do not compete with normal absorption. The fact that patients retained fairly constant defects of fat absorption over long periods despite exacerbations of intestinal symptoms accompanied by evidence of vitamin deficiency, and that they were cured without alteration of the fat defect, suggests that the deficiencies are not directly related to the fat defect. We are particularly interested in vitamin B_{12} but here the evidence for intestinal synthesis is incomplete, although we know it is needed by some intestinal organisms. It has been shown that patients with pernicious anæmia excrete appreciable amounts of this vitamin in the fæces, the amounts being of the same order as in the stools of normal persons. Extracts prepared from fæces, normal and pernicious, are active clinically and there is no doubt that the active material is vitamin B_{12} (Bethell *et al.*, 1948; Callender *et al.*, 1949; Spray, 1950). It has not so far been possible to determine whether the amount of vitamin B_{12} in the fæces may exceed that taken in the diet but it seems quite possible that this will prove to be the case.

Some animal work carried out by the present writer and his colleagues also suggests that bacterial infection rather than steatorrhœa *per se* brings about vitamin deficiencies. A macrocytic anæmia can be produced in rats by forming diverticula in the small intestine (Cameron *et al.*, 1949) and in these rats there is no histological change in the gastro-intestinal tract. Fat absorption studies were made on these rats and the results (Aitken *et al.*, 1950) show that although most of the rats did have some steatorrhœa, whether or not anæmia had developed, yet there were undoubtedly some anæmic rats without any fat defect. On the other hand all operated rats which were examined bacteriologically had a heavy infection of the small intestine with colonic flora. This suggests, though it does not prove, that bacterial infection is responsible for the anæmia; there is no indication that competition rather than a toxic action is concerned.

Conclusions

It is probable that the pathogenesis of pernicious anæmia is not simply a conditioned deficiency through loss of the intrinsic factor; there is likely to be at least one other element in the pathogenesis. There is some reason to think that this second element may be found in the small intestine. It is true that much of the argument is derived from conditions other than pernicious anæmia itself, but these are conditions in which a megaloblastic marrow is found and they must be accounted for. It may be thought outmoded in these days to invoke the intestinal bacteria at all, but there are some interesting parallels in other fields. For example it has been shown (Roine and Elvehjem, 1950) that guinea-pigs kept on a synthetic diet will not attain optimum growth unless given certain supplements, of no food value, which greatly increase the numbers of intestinal bacteria. Another pointer is the work on cobalt deficiency in ruminants (Gall *et al.*, 1949); cobalt-deficient sheep can be cured by feeding cobalt but not by injecting it and the cobalt-fed sheep have twice as many bacteria in the rumen contents as deficient animals. Abelson and Darby (1949) have taken this work further, using radio-active material, and shown that dietary cobalt may actually be incorporated into vitamin B_{12}. These are species other than man but it may be pertinent to remember some work of Davidson's (1928) which demonstrated very clearly the considerable changes of intestinal flora which occur in pernicious anæmia, and from which it seemed that if intestinal intoxication played a part in any disease it was in pernicious anæmia.

There is insufficient information to make any definite statement on the mode of action of vitamin B_{12}, but perhaps some speculation on the intrinsic factor is excusable. Intrinsic factor is associated with the upper end of the gastro-intestinal tract and the presence of an abundant flora with the lower end. This may mean that intrinsic factor has an antiseptic action in the sense that it prevents intestinal organisms from claiming the available vitamin B_{12}. Some recent work, not yet confirmed, may support this concept for it has been shown (Meyer *et al.*, 1950) that there are some similarities between intrinsic factor and lysozyme and it is claimed that vitamin B_{12} combines with lysozyme to form a complex unavailable to *E. coli* and *L. lactis* Dorner but which will cure pernicious anæmia in small doses. Complexes of vitamin B_{12} with this behaviour have been reported by other observers also. Gastric atrophy is another feature of pernicious anæmia on which there has been little speculation and one wonders whether, in view of the mucosal changes seen elsewhere which are attributed to vitamin deficiency, the gastric changes themselves are in part the result of a deficiency, so forming a kind of vicious circle leading to pernicious anæmia.

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Section of Comparative Medicine

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DISCUSSION ON DETERMINANT FACTORS IN THE INFECTIVITY OF MICRO-ORGANISMS

I. BACTERIA

Dr. David W. Henderson, *Microbiological Research Department Experimental Station, Porton, Wilts:* There are probably very wide differences of opinion on the definition of infectivity of micro-organisms. I choose to limit definition to the capacity to produce a manifest disease process in the host. In other words in the broadest sense it is the power of being "poisonous", and it is to be considered synonymous with the term virulence.

I feel that it is highly important at the outset to seal that definition by example. In conjuring up a conception of the degree of infectivity, there probably is in most of our minds a sense of invasive capacity—generally speaking there is the idea that the more invasive the organism, the more poisonous it will be. If we confine our definition of infectivity to the capacity of being poisonous, two examples may clearly show us first of all that the most toxic of organisms may have absolutely no capacity to invade the host tissue and, on the other hand, that a highly invasive creature can be so adjusted that no apparent damage to the host results.

A wandering tetanus spore may exist within the host possibly for years without causing damage. If, however, it becomes deposited in physical surroundings where the oxidation-reduction potential is sufficiently lowered, germination takes place; toxin is elaborated and absorbed, and the animal dies of acute tetanus the while the organisms remain strictly localized at the site of germination. In fact it can readily be shown that the danger to which the host is subjected is determined solely by the length of time the physical conditions at the site of germination remain capable of maintaining continued vegetation. In my opinion this wholly non-invasive organism must nevertheless be classified as highly infective.

An example in the entirely opposite direction is given by *B. typhosum* robbed of at least two antigenic components (the O and Vi antigens). Injected intraperitoneally into the mouse, this organism quickly establishes itself in the blood stream where it remains in great vigour for periods up to three weeks. The mouse likewise appears to remain in perfect health. This highly invasive organism must, however, be classified for our purpose in this Discussion as non-infective.

A teleological approach is always a dangerous one, but I think we are on fairly safe ground in assuming that in the evolutionary process saprophytism preceded parasitism. Accompanying such change to parasitism there can usually be observed fundamental changes in the internal economy of the parasite. Of these let us examine two examples: nutritional requirements and antigenic structure.

(1) NUTRITIONAL REQUIREMENTS

The view has been expressed that from the nutritional standpoint a change to parasitism involves a degenerative nutritional process. Thus, it has been argued that the most complete sense of independence is enjoyed by the autotrophe capable of synthesizing its total requirements from simple inorganic substances. Degeneracy, so called, gradually makes itself apparent through acquired dependence on organic products until we reach the deplorable state of the obligate parasite wholly dependent on the living cell.

Whether or not we choose to look on such differences as indicating a degenerative process, there are examples to show that the growth requirements of the parasite are more complicated than those of near relatives which, as far as we know, are strictly saprophytic. One might assume, therefore, that with a detailed knowledge of the growth requirements of the

pathogen, a key might be found to explain the difference between parasitism and saprophytism. Such information certainly will be most helpful, but unfortunately we already know that it does not solve the problem. Let me note three examples:

(*a*) *B. anthracis* is unique in being the only true pathogen within the very large group of spore-bearing aerobes in the Genus *Bacillus*. The nutritional requirements of the group as a whole are simple. Further, it can be shown that in comparison with certain strains of *B. subtilis*, *B. anthracis* has, if anything, simpler requirements. Nevertheless, grown in simple media *Anthracis* can be shown to go through the full cycle of growth from spore stage to spore stage, and at any point in the process it retains a full degree of virulence.

(*b*) The normal requirements of virulent forms of *B. typhosum* are not very complicated, and can be shown to be no more exacting than those of avirulent forms. Furthermore, both types can be "adapted" or "mutated" to grow in a simple ammonia medium containing a little carbohydrate, the while both forms retain in full measure their original characteristics.

(*c*) As a final example: one may note the spontaneous change from complete saprophytism to parasitism that occasionally occurs without as far as is known any accompanying change in nutritional requirements. Thus, it is recorded in the literature how such an innocent creature as *B. prodigiosum* can suddenly emerge as the causative agent of fatal septicæmia in man.

It is unlikely therefore that we will find a solution to our problem purely on the basis of nutritional requirements, and therefore other manifestations of the internal economy of the parasite will have to be examined. Now it is clear that by one means or another the metabolic activity of the successful invader differs from the saprophyte to the extent that, for longer or shorter periods, continued existence within the host is assured. In the final analysis the parasite, far from being "degenerate", probably is physiologically a much more complicated model of efficiency than the saprophyte.

(2) Antigenic Structure

In this respect the key to parasitism was apparently in our hands when, for example, the wide difference in antigenic structure between virulent and avirulent forms of bacteria was first recognized; clearly much has been explained on this basis alone. Once more, however, although perhaps less sharply defined than in the case of nutrition, differences in antigenic structure between virulent and avirulent forms of bacteria frequently fail to give a full account of differences in infectivity.

A classical example of this state of affairs is to be found in experimental infection with the pneumococcus. First of all I think it is true to say that more is known about the intimate antigenic structure and chemical composition of pneumococcal types than of any other organism. In addition, classical work has made it possible to transform one type into another both by *in vivo* and *in vitro* methods. Now it has been shown for example that, if a type pathogenic for mice loses its specific antigen, it automatically loses pathogenicity. It would appear, therefore, as if this antigen were the sole key to virulence. Unfortunately this is not so. Thus, if this basically virulent strain, now robbed of its specific antigen, is made to acquire the specific antigen of a type highly virulent for rabbits, it is virulent neither for the mouse nor the rabbit. However, made to reacquire its original specific antigen, virulence for the mouse is fully re-established. That, to say the least of it, is disconcerting, and it is obvious that factors other than specific antigen must be built up in the organism before the power of infectivity can manifest itself.

As a second example one may note recent experience in our own laboratories. My colleague Burrows has developed a technique for the induction of X-ray mutation in *B. typhosum*. Such mutation is characterized by nutritional deficiency, and many strange creatures have emerged. Among them are several that have lost the power of synthesizing purine derivatives such as adenine. Now these types, when supplied with the necessary substances, elaborate both O and Vi antigen. However, such mutants are certainly to be placed in the class of avirulent strains, for in fact the killing dose of living suspensions is nearly the same as the dose of killed suspension of a fully virulent strain. It seems, therefore, that we have here a clear demonstration of the fact that antigenic composition is not the sole key to infectivity.

Now in addition to those antigens that are intimately associated with the cell and play a part in infectivity, certain organisms produce soluble products quite distinct from the typical exotoxins of, for example, *Cl. tetani* that I mentioned earlier, that are also of importance. We may note two examples:

First of all, the "spreading factor" of McClean and Duran-Reynals now recognized as hyaluronidase. This enzyme is elaborated by a very wide variety of micro-organisms. In certain instances, as for example in certain streptococcal infections, it can be shown to play a dominant role in the outcome of infection. In others, as for example *Cl. welchii* infections, there is generally no detectable difference in the disease established by strains that do elaborate hyaluronidase, and those that do not.

Secondly, one may note the much debated role of "aggressins" in establishing the infectivity of certain bacteria. These substances were first described by Bail as only to be produced *in vivo* through some mythical host reaction on the organism. They were believed to be responsible for breaking down host defences, allowing the organism to invade and kill. If one takes *B. anthracis* infection as an example, cell-free tissue extracts of infected animals were in fact found to produce an effective immunity. Gladstone in recent years has firmly established that similar, if not identical, substances can be produced *in vitro*. (Here in parenthesis may I add the hope that once and for all the myth is dispelled that only the living host can induce the production of such substances.) Now it is highly probable that they do play an important part in infection provided always the strain producing them is in a position to take advantage of the situation. But, in a way closely paralleled by the role of the pneumococcus that I have outlined, one finds that completely avirulent strains of *B. anthracis* have produced these substances. Once again, therefore, "aggressin" production forms only part of the story of infectivity.

So far I have outlined a few of the intrinsic factors associated with the organism and its power of infectivity. I have chosen to do so in a sort of negative sense by pointing out that no single factor or group of factors determines infectivity as I have chosen to define it.

It is my opinion that extrinsic factors play an equally important role. Regrettably many of them are as yet ill-defined, but I would predict that, until such time as they have been explored further, our understanding of the initiation of naturally occurring bacterial disease will be far from complete. Let me take at random a few examples of the effect of such extrinsic factors.

In testing the virulence of anthrax strains, a not infrequent method is to inject the spore suspension in distilled water intraperitoneally in mice. In so doing great care must be given to the volume of liquid containing the spores that is injected. For example, if a 1·0 ml. volume is used, a very much higher death-rate is recorded than if the same number of spores is given in 0·1 ml. The reasons for this are not clear, but it may well be either a direct and systemic toxic action on the host, or a lytic action on the cells lining the peritoneum whereby substances essential for the germination of the spores are liberated.

This latter theory is given added support by some recent work in our laboratories on the role of surface active agents in enhancing the infectivity of anthrax spore suspensions. The most dramatic results are to be observed in the rat—an animal generally regarded as having a solid natural immunity to anthrax. Thus, it can be shown that the I.P. injection of 10^8 spores in 0·5 ml. distilled water is well tolerated by the rat, only a very occasional animal dying from specific anthrax infection. If, however, in place of distilled water a 1% solution of the kationic detergent, known commercially as Tergitol, is used, the LD 50 is obtained with about 100–1,000 spores; an enhancement in infectivity of at least 100,000 to one millionfold. Now the elucidation of this problem is far from complete, but first of all it seems as if the degree of activity of a detergent in this respect may be closely related to its lytic activity, and secondly it can be shown that certain naturally occurring body fluids, as for example mouse plasma, used in the same volume as with the Tergitol spore suspension, can produce nearly identical results. These two points suggest that within the peritoneum of the rat all that may be required is a suitable culture medium for the germination and development of the anthrax spore.

Enhancement of infectivity by other extrinsic agents, as for example hog gastric mucin, is now thoroughly established for a wide variety of organisms. Incidentally, the degree of enhancement of infectivity of anthrax spores in the rat by the use of mucin is closely similar to that produced by Tergitol. Nevertheless it can be clearly demonstrated that the mucin acts in an entirely different way from the Tergitol. The mode of action of the mucin is not proven, but it is being currently suggested in the literature that it increases tissue permeability in such a way that the would-be invader is given easy access to sites where it may readily multiply.

Irrespective of the precise mode of action of these two types of substance, it seems clear that they act synergically with the potential parasite to produce a degree of invasiveness of the mixture which in many instances closely approaches the theoretical limits, namely the induction of disease by a single parasitic cell.

These dramatic results are conditioned in large measure by the route of infection, and by the intimacy of contact between the parasite and the adjuvant. As far as the detergents are concerned in the enhancement of infectivity of *B. anthracis*, no effect is noted if the mixture is given intracutaneously, subcutaneously or by the intravenous route and only some relatively small effect is observed when the respiratory route is used. One can speculate as to why this is so, but supporting experimental evidence is lacking. A not dissimilar state of affairs exists in the case of gastric mucin. Certainly the intraperitoneal route is the one *par excellence*, but some action is claimed when other routes are chosen. However, the literature is far from

satisfactory on this issue, and there are certainly little data that would stand up to the cold analysis of the statistician.

The route of infection can certainly determine the type of host reaction as well as the type of disease that may manifest itself. In this latter connexion I would cite what I find to be a fascinating example.

Some years ago Stephenson and Ross, while working on problems of immunity to anaerobic infection, encountered a strain of *Cl. welchii* which, if suitably introduced into limb muscle, produced a classical type of experimental gas-gangrene the toxic symptoms of which could be effectively controlled by antitoxin. If, however, infection was initiated by the I.P. route, no amount of antitoxin could save the animals, and the evidence was that they did not die of a classical *welchii* toxæmia, but from a septicæmia in which no exotoxin was elaborated. Now this may be an extreme case, but in passing it is well to remember that the degree of success attending the antitoxic therapy of *welchii* infection of war wounds, most frequently of the extremities, has not been obtained in *welchii* infections of abdominal origin.

Reverting to the influence of extrinsic factors other than the host in determining infectivity, I should like to take one final example. The field of airborne infection consists almost wholly of a maze of unsolved problems. That such a means of infection was possible was proven experimentally some sixty to seventy years ago, but the determinant factors are as yet so completely unknown that we find ourselves arguing as to whether or not airborne infection is in fact an important issue in naturally occurring disease. It is clear that in the years to come experimental methods must be devised to elucidate this problem, and I suggest that the study of these issues will either alleviate our apprehension of the possible dangers of such a mode of infection, or more probably give us leads as to the causation of some of the greatest epidemics known to man. Three lines of attack that deserve immediate attention are:

(1) The role of particle size in determining infectivity according to the pathogen involved. For example, it may well be that for the initiation of a pneumococcal infection penetration of the infective particle to the deepest alveolar spaces is essential, whereas with neurotropic virus the deposition of particles on the olfactory nerve endings is the essential criteria for establishing infection.

(2) The menstruum in which the infective particles may be held will surely be found to play a very important role. I have already mentioned extrinsic factors that can be of the greatest importance in establishing an invader, and I would be surprised if in airborne infection this was not found to be of paramount importance.

(3) Finally, investigation will have to go much further on the possible synergic action of two or more potential invaders be they presented to the host simultaneously, or separately and by different routes.

II. VIRUSES

Professor W. I. B. Beveridge, *Department of Animal Pathology, University of Cambridge:* In discussing the process of infection by viruses, a useful starting point is to consider the fundamental difference between viruses and most other infective agents, namely, that viruses have to get inside susceptible cells in order to multiply. Not only do viruses have to get through the various physical and chemical outer defences of the host, find their way to susceptible tissue and get inside the appropriate cells, but they have to accomplish this hazardous and difficult task without the aids which many bacteria have developed for these purposes, such as active motility, protective capsules, exotoxins, coagulase, &c. These considerations would lead us to suspect that viruses possess special mechanisms, the most important of which would be means of (*a*) attaching themselves to the appropriate cells, and (*b*) penetrating the cell wall.

It is well established that a great many viruses have, in fact, a propensity for attaching themselves to host cells and the mechanism of this ability has been studied in bacterial viruses (phages), animal viruses and plant viruses. With both animal viruses and bacterial viruses, attachment may occur without penetration, and the fact that a virus attaches to a particular type of cell does not necessarily mean that cell is susceptible. There is also other evidence which I shall mention later which shows that we must regard attachment as a process distinct from penetration.

Attachment of virus to cells.—The phenomenon of virus hæmagglutination, which with most viruses involves the attachment of the virus to the red cell, provides a useful model for the study of this first stage of virus infection. Hæmagglutination has now been demonstrated with the viruses of influenza A and B, Newcastle disease and fowl plague, mumps, Horsfall's pneumonia virus of mice ("P.V.M."), Taylor's new influenza-like virus, which he calls "1233", and several neurotropic viruses infecting the brain of mice (mouse encephalomyelitis, Columbia SK and MM, meningo-encephalomyelitis, encephalomyocarditis and the Coxsackie virus.

The virus of louping ill attaches to red cells but hæmagglutination has not been demonstrated. Vaccinia, variola and ectromelia cannot be included in this list because with them the hæmagglutinating agent is distinct from the virus elementary body.

During recent years there has been a great deal of investigation carried out on the virus-cell interactions with the influenza group of viruses. I shall try to summarize the salient points.

The attachment of the influenza virus to the red cell or the cell of the respiratory mucosa has been considered to be of the nature of an enzyme-substrate union. The virus has the property of an enzyme in that it destroys the receptors on the cells while it remains unchanged itself. The substrate, that is, the receptors, has been characterized as mucopolysaccharide in nature.

This union between the virus and the red cell *in vitro* can be prevented by a variety of substances which are widespread in nature and in the animal body. Most of these inhibitors of hæmagglutination are regarded as analogues which compete with the receptors. They can be destroyed by the enzymic activity of the virus. However, hæmagglutination-inhibitors of this type are either not anti-infective, or only weakly so, that is to say, when mixed with virus most of them fail to prevent infection occurring in mice or chick embryos. Therefore their biological significance is uncertain.

Turning now from these substances which inhibit hæmagglutination by playing the part of the receptors on the red cell, we have to consider another mechanism by which the virus-cell union can be prevented, namely, by destroying the receptors on the cells by means of a suitable enzyme, which in so doing plays the part of the virus. Enzymes in filtrates of cholera vibrio can not only destroy the receptors on red cells and so render them unagglutinable by the virus, but they can also prevent infection in mice and chick embryo (Stone, 1948).

As a result of work along these lines, it has been assumed that the destruction of the receptor by the virus was an essential step in the invasion of the cell. However, this view is now open to doubt. De St. Groth and Graham (1949) have shown that infection can proceed normally in chick embryos or in mice after the receptors on the cells concerned have been rendered resistant to the destructive action of the virus enzyme by previous treatment with periodate, which modifies the receptors in such a way that the virus still attaches to them but cannot destroy them.

No doubt normally enzymic destruction of receptors does take place, but it now appears that this may be only incidental to the process of infection. It is now questioned whether even the enzyme-substrate absorptive process plays an essential role in infection.

Whatever may be the true facts with influenza, it seems definite that the attachment mechanism used by Horsfall's "P.V.M." virus has nothing to do with enzymic action, for with this virus no enzymic activity toward its receptors has been demonstrated. Here the union is thought to be an electrolytic one (Davenport and Horsfall, 1948).

Penetration of cell walls by viruses.—There has been little direct investigation on this stage of infection because it is difficult to find an approach.

Merling (1949) has studied penetration of bacteria by bacterial viruses. He used the electron microscope but was not able to throw much light on what happens.

It has been suggested that penetration by viruses takes place by the same mechanism as does penetration of colloidal particles, but I doubt if this idea helps very much. There are canals running through the walls of the cells of the so-called striated layer lining the intestine. The function of these canals, which are about 0·5 μ in diameter, presumably is to allow entry of colloid-sized particles from the intestine. The transport through the canal is probably accomplished by means of electrical forces. I do not know whether similar canals exist in other cells.

In some instances penetration of the cell probably takes place by phagocytosis. This is the method by which Fenner (1949) believes the virus of mouse pox gets into cells of the liver and spleen of mice.

In summary then, our knowledge of how viruses penetrate cell walls is practically nil.

Multiplication of virus inside the cell.—After the virus has got inside the cell, the course of the infection may still be subject to certain outside influences as is shown by the phenomenon known as "interference". This term was originally employed to describe the effect of one virus in preventing or limiting the infection by a second virus inoculated about the same time. Now the term is also applied to the suppression of infection by agents such as inactive homologous virus, and this is the only aspect of the interference that I think is relevant to this Discussion. I would emphasize that here we are concerned not with hæmagglutination but with infection of a susceptible host.

A lot of investigation has been carried out on the interfering action of ultraviolet-irradiated influenza virus on active influenza virus in the chick embryo (Henle and Rosenberg, 1949). Another example of interference which has been closely studied is the effect which the polysaccharide of Friedländer's bacillus type B has on the infection of the chick embryo

by mumps virus, and on infection of the mouse by Horsfall's "P.V.M." (Ginsberg and Horsfall, 1949).

The Friedländer polysaccharide has an interfering action on infection by mumps or "P.V.M." even when administered four days after the virus, and irradiated influenza virus has a suppressing effect when given as long as three hours after inoculation of the active virus, that is, well after the virus has invaded the host cells. The Friedländer polysaccharide does not prevent the attachment of the virus to the cell, nor combine with the virus, nor in any way react with it outside the cell. The interference with the course of infection, at least with these two systems, is quite definitely not due to prevention of attachment or penetration of the virus. The interference concerns intracellular processes and is probably due to prevention of some phase of reproduction rather than to prevention of release of virus from the cell.

Incidentally, there is no interference between the influenza group of viruses on the one hand and the viruses of mumps and "P.V.M." on the other, which shows that the interfering effect is highly specific and not due to a general interruption of the metabolic processes of the cell.

The excessive dose effect.—Keeping these fundamental considerations of virus-cell relationships in the back of our minds, I would like now to discuss an interesting dosage effect that has been observed with several viruses, namely, that very large doses of virus may produce less severe infection than moderate doses. I shall refer to this as the "excessive dose effect". Probably these observations are not all manifestations of the same underlying mechanism, but I think the concept of the excessive dose is a useful idea around which to discuss several factors influencing the infectivity of viruses. I shall first list the examples and then discuss the probable explanations.

I. *Rabies*: The first observation of this nature was made by Pasteur with rabies. Not only did he notice that often suspensions of rabbit-cord virus in large doses produced rabies less regularly than small doses, but he carried out experiments which demonstrated this point (Pasteur, 1887).

II. *Influenza*: The best known and most studied example of the excessive dose is that influenza virus when inoculated in large doses into the allantoic cavity of the chick embryo produces a lower yield of virus than when smaller inocula are used (Henle and Chambers, 1941).

III. *Vaccinia*: Vieuchange (1940) showed that concentrated suspensions of infected rabbit brains produced much less severe reactions when inoculated into the skin than did the same material used more dilute. Similar results were obtained with calf lymph virus.

IV. *Distemper*: Green (1945) showed that distemper virus, after passage through ferrets, has lowered virulence for dogs, and he and others have found that small doses of this "ferret virus" more often lead to severe disease in dogs than do larger doses.

V. *Rinderpest*: Dr. J. T. Edwards (personal communication) has found that a 1 in 125 suspension of infected ox, goat or rabbit spleen is much more likely to set up infection in rabbits than a 1 in 5 suspension. He observed a similar effect when goat-adapted rinderpest virus was titrated in cattle.

VI. *Homologous serum jaundice*: There is a widely held opinion that this disease is more likely to follow very small doses of serum than very large doses. I do not know of any direct experimental evidence on this point.

VII. *Bluetongue in sheep*: In 1905 Theiler found that when he passaged this virus in sheep it caused during the first 10 passages a severe disease with 10% mortality, as it did in the field, but on further passage the disease was mild and caused no mortality. This sheep passage virus has been used extensively as a vaccine (Du Toit, 1929). It is contrary to general experience that serial transfer in a particular species of animal should result in genetic attenuation of a virus for that animal, and I suggest this may be another example of the excessive dose effect. Some support is lent to this hypothesis by recent observations that after passage in sheep for forty-five years, the virus can sometimes give rise to severe reactions, though no experiments have been reported using small doses (Neitz, 1948).

It might be misleading if I were not to mention that there are some viruses with which attempts have been made to demonstrate the excessive dose effect without success. These are mumps, Newcastle disease, Japanese B encephalitis, louping ill and the psittacosis group when grown in the chick embryo.

Possible explanations of the excessive dose effect.—In some instances the explanation of the excessive dose effect may be that antibody is present together with virus in the tissue suspensions used as inoculum. It is well known that neutral mixtures of fairly concentrated virus and antiserum often become infective if they are diluted. Vieuchange brought forward experimental evidence showing that this was probably the explanation in his work with

vaccinia. His virus suspensions were prepared from the brains of rabbits dying three or four days after inoculation, which is earlier than antibodies can usually be demonstrated. Oerskov and Anderson (1938) carried out experiments which suggested that local antibodies may be present even as early as the second day of vaccinia infection when massive inocula have been given, but not till much later when more dilute inocula have been used.

This explanation of the excessive dose effect as being due to antibody in the inoculum is more plausible when applied to Pasteur's work with rabies where the rabbit-cord virus was harvested at least a week after inoculation, and with bluetongue which was passaged at intervals of over a week, and homologous serum jaundice where the infective serum may be taken many weeks after inoculation. In this connexion it will be recalled that sometimes when animals die from infection with a virus with which they have been inoculated it is not possible to demonstrate the virus after death. These failures to detect virus have been attributed to the presence of antibody.

A second possible explanation of the excessive dose may be that the inoculum contains virus-neutralizing substances other than antibody. Non-specific virus-neutralizing substances have been demonstrated in body fluids and tissue extracts by several workers recently (Burnet, Lush and Jackson, 1939; Gard, 1944; Koprowski, 1946; Utz, 1948/9; Smith, 1949; Ginsberg and Horsfall, 1949). Such substances may be present in sufficient amount to prevent or lessen infection when concentrated suspensions are used as inocula but they mostly lose their action after moderate dilution. Under this head may also be mentioned the fact that some viruses become bound to tissue components. With some plant viruses so little "free" virus may be present in suspensions that grafting may be necessary in order to transmit the disease. Escape from antibody or other harmful substances in the tissue extract is probably also the explanation of why some Rickettsiæ increase in virulence for guinea-pigs during the first few passages in chick embryos.

With influenza virus in the allantoic cavity of the chick embryo, there can be no question of antibody, nor has any virus neutralizing substance been demonstrated in eggs. The explanation which was first accepted for the lowered yield of this virus which followed large inocula as compared with small, was that the inoculum contained virus which was degraded by age and which interfered with the active virus. The effect was obtained if the seed virus had been harvested forty-eight hours after inoculation but not if after twenty-four hours. The same effect could be obtained by adding irradiated virus to small inocula of active virus (Henle and Henle, 1943).

The Scandinavian workers von Magnus (1947) and Gard, von Magnus and Svedmyr (1947) have shown that the mechanism is not quite as was at first envisaged. They found that when influenza virus is passaged in eggs using undiluted allantoic fluids as inocula, the resultant "virus" has a low infectivity, or is even non-infective, for both mice and chick embryos when inoculated undiluted, though it is capable of killing mice when diluted 1 in 10 or 1 in 100. They showed that this is due to the production of two types of virus particle, the normal one and another which is non-infective from the start. This second one has an interfering action against the normal virus. These workers considered that when there is an excessive inoculum, too many virus particles invade each cell with the resultant shortage of some essential substrate and production of "incomplete" virus.

A mechanism of this type—blockade by non-infective virus—might operate in some others of the examples of the excessive dose effect which have been cited.

These three possible explanations of the excessive dose effect as being due to the presence in the inoculum of substances which are harmful to the growth of the virus, but only in low dilutions, are each based on experimental evidence. A further explanation has been suggested in the case of attenuated viruses, but, as far as I know, this one does not rest on experimental evidence. It has been suggested that when large inocula are administered, most of the susceptible cells are immediately infected by the attenuated virus, but when small inocula are introduced the virus may reproduce for many generations in the inoculated animal and this provides an opportunity for a more virulent mutant to occur.

I think these factors which I have mentioned have significance in the infectivity of viruses that goes beyond the examples of the excessive dose effect cited. For example, failure to isolate a virus and establish it in a new host might sometimes be due to inoculation being made with too concentrated suspensions. So far as one can generalize, I should think that the inocula likely to be the most infective would be material taken early in the course of a rapidly developing case of the disease, made into a suspension of about 1 in 100 in one step and inoculated without delay. Any adverse influences which it may be subjected to in the handling not only lower the titre but, what is probably more important, may produce inactive virus which will interfere with the remaining active virus. Nevertheless, when a virus is inoculated into a new host which it can only infect successfully by undergoing modification, the most essential requisite may be to administer a massive dose so as to provide the maximum opportunity for the desired mutant to arise.

Before leaving this subject it is worth noting that the excessive dose effect may be cumulative over several passages. This has been demonstrated clearly with influenza in the egg and is probably implicit in the work quoted on vaccinia and bluetongue. Conversely, several rapid passages under optimum conditions are often required to regain maximum infectivity of a virus that has been subjected to adverse influences. This may be due to the avoidance of the factors which bring about the excessive dose effect.

Attenuation and adaptation.—By "attenuation" to-day we usually mean a genetic change in the organism associated with decreased virulence for a particular host. However, earlier virus workers, and some present-day ones, speak of attenuating a virus by some chemical or physical treatment, just as one might speak of partly detoxicating a toxin. Attenuation in this sense is not genetic, but neither is it purely a matter of lowering the number of infective virus particles. I suggest that this form of attenuation is due to the creation of a mixture consisting of a small number of infective particles together with many others that are non-infective but capable of exerting an interfering effect and an antigenic effect.

But "attenuation" as we usually employ the term to-day is a genetic process, associated with adaptation to a new host and decreased virulence for the original host. Until quite recently the general view was that adaptation to a new host depends on the occurrence of a mutant which is favoured by the new environment and so grows more rapidly and displaces the original type. However, there is a different type of genetic variation which must now be taken into account. Recent work with bacterial viruses has shown that these viruses can reproduce by a sexual process, which involves a recombination of the characters of two parent strains. The progeny of such "crossbreeding" between two bacterial viruses may show a new host range (Hershey and Bronfenbrenner, 1948).

Very likely it is possible for two strains of an animal virus to "crossbreed" in this way. Recombination of characters from different strains may be the method by which epidemic strains arise following the mixing of populations. Mixing of populations of people or animals would provide opportunities for the mixing and "crossbreeding" of strains of low virulence and this may produce a strain of high infectivity and high virulence.

Another interesting possibility is that with knowledge of this method of reproduction we may be able to produce new strains which can infect new hosts. For example, a mixture of several different strains of virus, none of which can themselves grow in a chick embryo, might give rise to a strain which can grow in this host. In fact possibly this has already been done inadvertently. Traub and Schneider (1948) inoculated a mixture of 10 strains of foot-and-mouth virus into the chick embryo thinking that perhaps one of the ten might be capable of growing there. He obtained growth of a strain which however did not correspond exactly in character with any of the strains inoculated. He does not seem to have considered the possibility of its being a recombinant.

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Section of Obstetrics and Gynæcology

President—LESLIE WILLIAMS, M.D., M.S., F.R.C.S., F.R.C.O.G.

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DISCUSSION ON HYSTERECTOMY

Mr. C. W. Kimbell[1]: It is some considerable time since this Section reviewed the subject of hysterectomy. The last extensive British Survey of abdominal hysterectomy by Read and Bell covered the ten-year period 1922–31. This report is a joint survey of almost 3,500 abdominal hysterectomies performed by seventeen operators at the Samaritan Hospital for Women, London, during the twenty-one-year period 1928–48. This paper is a limited review; full details we hope to publish elsewhere.

I should like to suggest that the term panhysterectomy be abolished in favour of the term total hysterectomy with or without salpingo-oophorectomy.

The patients were usually admitted for two days' rest in hospital preceding operation, receiving a general physical examination and such other investigations as were deemed necessary, together with any pre-operative treatment needed. Latterly this has included blood transfusions. Obesity and hypertension did not preclude operation. There were two deaths on the operating table, one under open ether and chloroform and the other following confusion over gas cylinders.

All patients were catheterized immediately pre-operatively and received some form of vaginal preparation.

Indications for operation.—These follow the pattern found in other published series, fibromyomata heading the list.

Incision.—Almost exclusively this was a mid-line suprapubic incision, other scars being excised as a rule.

Position of the patient.—Moderate Trendelenburg with shoulder supports is the general rule, and in this series we did not find any record of pressure palsies, although we have since had 3 cases.

Skin towels.—Wounds appeared to do equally well whether these were used or not.

Injury to the urinary tract.—These injuries were surprisingly rare, six in the series.

Subtotal v. *total.*—In almost one-third of the cases the subtotal operation was performed, this high incidence being due to a minority of operators, the remainder performing the total operation. At times a preliminary subtotal hysterectomy was performed, the operator then proceeding to complete the total operation. The Worrall operation of reaming out of the cervix has not been practised.

Conservation of ovaries.—The staff are divided as to the desirability of routine ablation of the ovaries, though all are agreed that pathological ovaries should be removed. In general ovaries are conserved.

[1]Summary of Joint Paper by C. W. Kimbell, M.B., Ch.B.N.Z., F.R.C.S.Edin., M.R.C.O.G., and E. Harford Rees M.B., B.S.London, M.R.C.O.G., F.R.C.S. The full paper has been offered to the Editor of the *Journal of Obstetrics and Gynæcology of the British Empire.*

Bilateral salpingectomy.—We do not, as a group, perform hysterectomy in cases where both the fallopian tubes have been removed, unless there be an added reason such as menorrhagia.

Ligature material.—A few of the staff use thread for the main pedicles, but it is best avoided near the vaginal vault.

Operative technique.—The routine steps of hysterectomy are to-day standardized and well known. The following points are worthy of comment:

(1) Never clamp or ligature without inspection first.

(2) It is good practice to ligature uterine and ovarian arteries doubly.

(3) It is helpful to incise the precervical fascia thus facilitating freeing of the bladder.

(4) The vaginal angles should be carefully ligatured, neglect being a common cause of hæmorrhage.

(5) It is useful to anchor the vaginal angles to the uterine arteries thus supporting the vaginal vault in an attempt to avoid vault prolapse. Alternatively the round ligaments can be utilized. Whilst we have no figures of the incidence of subsequent vault prolapse, our impression is that it has been a rare sequel.

(6) The uterus should be opened on removal. Failure to observe this rule will account for the occasional case of a carcinoma of the cervix or body of the uterus being missed until the abdomen is closed.

(7) Careful hæmostasis and peritonization are essential.

Should the vault be closed?—In the absence of troublesome oozing where obviously drainage should be provided, patients do equally well whether the vault is closed or left open. It is of no moment whether the sutures pass through the vaginal wall or not.

Deep tension sutures.—The majority employ these sutures, although hæmatoma has occurred. I (C. W. K.) believe that coapting sutures through the skin and fat are preferable, and also that the recti muscles should be approximated with a few catgut sutures.

Rectus sheath.—As a group, continuous catgut is employed unless it is considered advisable to use interrupted sutures in the presence of sepsis and malignancy.

Skin.—Clips are used mostly, but a few use continuous unabsorbable sutures. The results appear to be the same.

Intravenous therapy.—This is employed before, during or after operation, as indicated.

Reactionary hæmorrhage.—This occurred twenty-one times in our series. Routine post-operative swabbing of the vagina on the operating table sometimes enables this to be detected before the patient leaves the table.

Post-operative shock or hæmorrhage.—There were 7 deaths from shock or hæmorrhage in the total, and 5 in the subtotal hysterectomies.

Associated operations.—Such operations included vaginal repairs, herniotomy repair of ventral hernia, bowel operations, &c., and totalled 109 (80 in total hysterectomies and 29 in subtotal). There were only two deaths, one in which colostomy was performed, the patient dying of cachexia on the fourteenth day and the other associated with excision of the distal portion of the sigmoid colon, death occurring on the fourteenth day from ileus. The risk is thus negligible.

Appendicectomy.—Two operators in this group performed almost routine appendicectomy, the remainder only removing the appendix if diseased.

Total hysterectomy and appendicectomy	502	
Subtotal „ „ „	58	
Deaths in Total group	6	1·2%
„ „ Subtotal group	1	1·7%

Although these figures suggest an additional risk, in only one case can the death be attributed directly to the appendicectomy, intestinal obstruction supervening owing to adhesions to the appendicular scar (post-mortem finding).

Morbidity.—It is regrettable that no internationally agreed standard of morbidity exists and it is to be hoped that the World Health Organization will remedy this lack. We have chosen one main standard:

Fever of 100° F. or over for two or more days, excluding the day of operation.

Total hysterectomies	52·8%
Subtotal „	33·7%

Causes of morbidity.—The majority are unspecified and are probably due to urinary infection or vault hæmatoma. Proven causes include urinary, respiratory tract infection, wound sepsis or hæmatoma, pulmonary emboli, thrombophlebitis, anæmia and tonsillitis.

Other post-operative complications.—The following are of interest:

	Cases
Vesico-vaginal fistula	1
Deliberate excision of ureter	1
Ureteric injury	3 (one fatal)
Injury to bladder	3 (all subtotal hyst.)
Burst abdomen	13 (5 in malignant cases)
Pulmonary embolism (as recorded)	46 (9 cases fatal)
Intestinal obstruction	7 (2 deaths)
Paralytic ileus	9 (5 deaths)

Mortality.—Search of the recent literature shows an increasing tendency to perform the total operation, and also decreasing mortality rates.

SAMARITAN HOSPITAL FOR WOMEN

2,569 Total hysterectomies	35 fatal cases	1·4%
910 Subtotal „	15 fatal cases	1·6%

ANALYSIS OF DEATHS (SAMARITAN HOSPITAL)

Total hysterectomy. 35 in 2,569 cases (1·4%)

Shock and hæmorrhage	7
Pulmonary embolism	6
Pneumonia	5
Ileus	4
General peritonitis	2
Intestinal obstruction	2
Cerebral vascular accidents	2
Cellulitis	2
Death on the operating table	2
Sepsis	1
Uræmia	1
Cachexia	1

Subtotal hysterectomy. 15 in 910 cases (1·6%)

Shock	5
Pulmonary embolism	3
Peritonitis	3
Ileus	2
Coronary thrombosis	1
Pneumonia	1

It is probable that the higher rate in the Subtotal series is because this operation is often performed when the difficulty of the case renders the total operation too hazardous. Several of the early deaths were due to paralytic ileus, which were thought to be cases of obstruction. Improved therapy and recognition of this condition has resulted in less interference. Since 1942 the analysis is as follows:

Operation	No. of cases	Deaths	Mortality
Total hysterectomy	970	4	0·4%
Subtotal „	391	5	1·3%

The Mayo Clinic figures are of great interest:

January 1, 1937, to December 31, 1945

Operation	No. of cases	Deaths	Mortality
Total hysterectomy	5,115	32	0·6%
Subtotal „	1,147	8	0·7%
Vaginal „	2,942	14	0·5%

The accuracy of any analysis must depend on the quality of the notes recorded which are often incomplete. The necessity for detailed and careful notes with fuller post-operative progress reports is emphasized.

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MEIGS, J. V., and STURGIS, S. H. (1947) Progress in Gynæcology. London, p. 428.

Mr. C. M. Gwillim: Vaginal hysterectomy is an old operation which was largely abandoned as the abdominal approach, with its wider scope, became more successful. It fell into disrepute because it was often used in mechanically unsuitable cases and without the advantages of modern technique and the clearer anatomical knowledge of to-day.

Nevertheless, it was not entirely forgotten. The Viennese, especially those of the Schauta School, retained and improved it. They developed that detailed and accurate knowledge of pelvic anatomy as approached from below, which is the essential for success. Peham and Amreich's *Operative Gynæcology* is still the most valuable guide to the vaginal operator.

The operation has returned to favour because of its obvious usefulness in cases of uterine disease complicated by prolapse. There are still some who would combine a repair with radium or with an abdominal operation. This seems hardly logical, in such cases, if the mortality of vaginal hysterectomy and repair is not greater than that of Fothergill's operation alone.

Vaginal hysterectomy for non-malignant conditions may be classified in three groups:

(1) Simple vaginal hysterectomy for disorders of the uterus.

(2) Vaginal hysterectomy and repair for uterine disease associated with uterine or vaginal prolapse.

(3) Vaginal hysterectomy and repair for uncomplicated prolapse.

I shall deal mainly with the first group.

The advantages of simple vaginal hysterectomy are:

(*a*) There is no abdominal wound. From the patient's point of view, no wound at all.

(*b*) There is practically no post-operative pain.

(*c*) There is less danger of intestinal obstruction and ileus than in the abdominal approach.

(*d*) The operation is free from shock and, when the adrenaline infiltration technique is used, is almost bloodless.

(*e*) There is a better anatomical approach and there is greater visibility of the stages of the operation. This statement will surprise those who have not seen the vaginal dissection, and particularly those mistaken critics who talk of "operating through a keyhole in the dark".

(*f*) The patient may get up early after the operation with neither fear nor discomfort and without risk.

(*g*) Immediate and total convalescence are both much shortened. Not having an abdominal wound, the patient can the more readily be persuaded to return to normal life and full activity.

The points *against* the operation are:

(*a*) The abdomen cannot be explored.

(*b*) It is not always possible to remove the ovaries.

(*c*) A narrow vagina may make the approach impossible without resort to a Schuchardt incision.

(*d*) Large tumours or adherent masses cannot be dealt with.

It is true that with increasing experience the range of the operator is greatly extended, but it must be remembered that unnecessary difficulties may discourage the surgeon and bring the operation into undeserved disrepute. Cases of endometriosis or where a ventro-fixation or a ventro-suspension has been done are best approached through the abdomen.

The indications for simple vaginal hysterectomy are:

(*a*) Functional uterine bleeding.

(*b*) Fibroids.

(*c*) Adenomyoma.

Under the heading of *functional uterine bleeding* come those cases which at various times have been described as menopausal menorrhagia, metropathia hæmorrhagica, fibrosis uteri, sub-involution and chronic metritis. In these cases the uterus is slightly enlarged and often retroverted. If endocrine therapy fails, they are best treated by vaginal hysterectomy, rather than by the use of radium or deep X-rays to induce an artificial menopause.

Hysterectomy has the advantage of the complete removal of a pathological organ. The danger of leaving the cervix is shown by Pund and Auerbach (1945, *Amer. J. Obstet. Gynec.*, **49**, 207), who found 3·9% of 1,200 uteri removed by total hysterectomy showed early carcinoma.

It has been shown that carcinoma of the corpus is not prevented by radiation and may even develop more frequently in this type of case, especially when the menopause is delayed.

It is generally agreed that surgery is preferable to radiation in women under 40. From these observations it would seem wiser to employ surgery in the later age-group also. The proper use of radium implies anæsthesia and curettage and the use of a vaginal pack and self-retaining catheter. A firm pack causes discomfort which is at least equal to that caused by vaginal hysterectomy. Too light a pack may allow of slipping of the radium container and a consequent radium burn. Hæmorrhage may follow the use of radium, either from overdosage or underdosage. Rarely a radium burn may result in a fistula. The mortality from the use of radium is variously claimed as nil, 0·3% and 2%.

Fibroids can be dealt with most satisfactorily by vaginal hysterectomy. The problem is essentially one of mechanics. Where the fibroids are small the operation has no undue difficulty. As the operator progresses in experience, skill and judgment, he will find himself removing larger and larger masses. With hysterectomy and myomectomy it is possible to extract fibroids up to the size of a three or four months' gestation without difficulty. Such practices, however, are unwise until the operator has become very experienced.

Adenomyoma and adenomyosis, when uncomplicated by adnexal endometriosis, present similar problems to those of fibroids.

The cases presenting prolapse in addition to uterine disorder are those which first persuade an operator to try vaginal hysterectomy. There is the obvious saving of a double or second operation and the lax vagina with a prolapsing cervix renders the approach easy and the results encouraging.

The operation depends for its success on a meticulous attention to anatomical and technical detail. Apparently minor points are of the first importance. Hurried, scamped or slapdash work is likely to be disastrous.

[A film was shown to illustrate the main features to be stressed.]

The use of an injection of dilute adrenaline in saline around the cervix is of great assistance in showing up the tissue planes and in securing hæmostasis. Personal experience of this method over fifteen years has been without mishap, but care needs to be constant. No small bleeding points should be left unligated. The solution must not be used with chloroform, trilene or cyclopropane anæsthesia; nor must it be given to patients with cardiac disease and the injection must not be made into a vein.

The operation must be conducted with meticulous care and deliberation. Every structure must be seen and accurately identified before it is clamped or cut. Not infrequently the ureters can be seen; occasionally they are adherent to the cervix.

All pedicles must be securely and doubly ligatured. There must always be a ligature other than that by which the pedicles are approximated. Care must be taken that the needle is inserted distal to the hæmostatic ligature when the second approximating ligature is inserted.

Aneurysm needles, rather than clamps, should be used for tying pedicles. They take much less room and enable the ligature to be tied before the artery or ligament is cut. Hæmorrhage arising from a slipped or springing clamp can be disastrous.

The following table shows the results in cases operated on personally in the Samaritan Hospital from 1931 to May 1950 and in St. George's Hospital from 1935 to May 1950.

		Deaths	Mortality %
Total abdominal hysterectomy for non-malignant condition	785	3	0·38
Simple vaginal hysterectomy	163	0	—
Vaginal hysterectomy and repair	356	4	1·12
Fothergill's operation (1940-48)	405	7	1·7

The deaths and mortality percentages present several interesting features. It will be seen that there has been no death in cases of simple vaginal hysterectomy. The mortality for total abdominal hysterectomy for non-malignant conditions was 0·38%. The two series cannot be claimed to be comparable but it would seem that simple vaginal hysterectomy is at least as safe as abdominal hysterectomy.

On the other hand, where a repair operation is done at the same time, the mortality is almost three times that of total abdominal hysterectomy. As these findings appear to be startling, the result of Fothergill's operation performed by my colleagues at the Samaritan Hospital from 1940–48 are given for comparison. From this it would seem that the mortality for vaginal hysterectomy and repair is not greater than that for repair alone.

Mr. A. C. Bell: *Relative merits of the total* versus *the subtotal operation in benign conditions of the uterus.*—In the last twenty-five years, much has been written on the relative merits of the two operations. Some gynæcologists, including the late Herbert Spencer, preached that total hysterectomy should always be employed when the uterus required removal for fibroids. I believe there is still a limited place for the subtotal operation, provided that there is no risk of the residual cervix requiring subsequent medical or surgical treatment. An increasing number of gynæcologists, including myself, favour the total operation in women who have borne children or had miscarriages, as in such patients the cervix is potentially unhealthy.

Coning out the cervix or endocervical cauterization is not a satisfactory alternative to the total operation, for it does not remove the tissue from the vaginal portion of the cervix, and is, therefore, no protection against the subsequent development of carcinoma of the squamous-celled type which starts on the vaginal portion rather than in the cervical canal.

Disadvantages to each operation: The chief disadvantage of the subtotal operation is that leaving the cervix in situ predisposes to subsequent disease of that organ. The fact is, however, that in nearly every instance, an unhealthy cervix is present at the time of the subtotal operation, and therefore can be anticipated. It is seldom that nulliparous cervices give rise to subsequent trouble. The extent of trouble with the residual cervix is well known to those in charge of a large out-patient department; a considerable number of residual cervices will require in-patient treatment. In a review of hysterectomies at the Chelsea Hospital for Women, 1922 to 1931, undertaken and recorded by Charles Read and myself, 45 patients were admitted with sequelæ of the subtotal operation, whereas only 7 were admitted following the total operation. The most serious sequel of the subtotal operation is the stump carcinoma, of which there were 10 cases in our series. As far as I know, no comprehensive follow-up of subtotal hysterectomies over a twenty-year period has been made, and no reliable figures exist as to the incidence of stump carcinoma. Because of this difficulty, it is usual to compare the number of stump carcinoma cases with the number of cervical cancers in the intact uterus—a figure of 4 to 5% has been given by some authors. The possible development of stump carcinoma is the chief disadvantage of the subtotal operation.

There is another less common objection to the subtotal operation—when it is undertaken under the mistaken impression that the condition is benign, whereas an unsuspected carcinoma of the cervix or body exists. Unless a previous curettage has been performed, the bodies of all uteri removed by subtotal hysterectomy should be opened for inspection before the abdomen is closed. If this rule is observed, the residual cervix and ovaries can be removed forthwith, should carcinoma of the body exist. On the other hand, there is no redress for the cutting across a carcinomatous cervix. The remedy lies solely in careful pre-operative diagnosis.

The disadvantages of the total operation lie chiefly in the technical difficulties which may involve injury to the bladder and ureters. There were only three post-operative fistulæ encountered in our review of the hysterectomies. Although I have done many hundred total hysterectomies, I have only once produced a ureteric fistula, and that in an old tuberculous case. In order to avoid injury to ureters, the uterine artery clamps should be placed parallel to, and closely applied to, the cervix, with the point of the forceps well down to the vaginal angle. Unless there is bleeding or displacement of the uterus by a cervical or broad ligament tumour, it is unnecessary to isolate or even identify the ureters before clamping the uterine vessels.

Injury to the bladder in a total hysterectomy can best be avoided by good exposure, and displacing the bladder well down by gauze dissection. The bladder should be displaced at least ½ in. below the site where it is intended to open the vagina. Having opened the vagina, I have always found the safest and most satisfactory method of dealing with the angles of the vagina is by placing an angled Mayo-Oschner forceps with the lower blade inside the vagina, the upper blade being placed *internal* to the lower end of the uterine clamp. If the original uterine clamps are properly placed, there is no danger of injury to the ureter when this method is used. In clean cases, the vaginal vault is closed. Although the post-operative morbidity of total hysterectomy is said to be slightly higher, it is not a significant factor.

As regards late sequelæ of the total operation, apart from the occasional fistula, I will repeat what Read and I said in 1933—"they are few in number and innocent in nature".

I have found no support for the statement that dyspareunia is likely to occur after the total operation. Prolapse of the vaginal vault should not occur if the severed uterine ligaments and vessels are anchored into the vaginal angles at the time of operation. In the occasional case when vaginal prolapse already exists in a patient in whom it is necessary to remove the uterus, the operation of choice would be a vaginal hysterectomy combined with a repair from below.

Table I gives statistics from the Chelsea Hospital for Women relative to the two operations—the first period, 1922–31, the second period, 1933–45.

TABLE I.—HYSTERECTOMY

Chelsea Hospital for Women

	1922–31		1933–45	
	Total	Subtotal	Total	Subtotal
Number of cases	605 (25·8%)	1,739 (74·2%)	1,703 (47·3%)	1,899 (52·7%)
Deaths	19	37	26	26
% Mortality ..	3·1%	2·1%	1·5%	1·4%

The two significant points that appear from these figures are the larger proportions (47%) of total hysterectomies performed in the more recent series—also the increased safety of both operations, particularly total hysterectomy—the mortality fall for that operation actually being greater than for the subtotal.

This relative lower mortality is also recorded in the Mayo Clinic figures for 1937–45, where the total hysterectomy mortality of 0·6% is exceeded by the subtotal hysterectomy mortality of 0·7%.

These American figures compare with the Chelsea hysterectomy figures for fibroids:

TABLE II.—HYSTERECTOMY FOR FIBROIDS

Chelsea Hospital for Women

	1922–31		1932–45	
	Total	Subtotal	Total	Subtotal
Number of cases	172 (12·9%)	1,159 (87·1%)	740 (33·5%)	1,466 (66·5%)
Deaths	5	24	5	18
% Mortality ..	2·9%	2·0%	0·68%	1·2%

Here again there is an increased tendency to perform total hysterectomy for fibroids, and the mortality of under 0·7% is lower than the corresponding mortality for fibroids treated by the subtotal operation.

There is no doubt that improved technique, aided by sulphonamides, antibiotics, anti-coagulants and other advances in surgery, has rendered the operation of hysterectomy considerably safer in the last twenty years; particularly interesting are the low mortality figures for total hysterectomy. Pulmonary embolism still remains the commonest cause of mortality in either operation (Table III).

TABLE III.—HYSTERECTOMY

Chelsea Hospital for Women—1932–45 (*Inclusive*)

	Total	Deaths	Mortality	Subtotal	Deaths	Mortality
1932	76	—	—	206	3	1·5%
1933	117	3	2·6%	170	5	2·9%
1934	127	3	2·4%	192	3	1·6%
1935	127	3	2·4%	164	3	1·8%
1936	184	5	2·7%	173	1	0·6%
1937	187	3	1·6%	189	3	1·6%
1938	116	1	0·9%	123	2	1·6%
1939	135	1	0·7%	153	1	0·7%
1940	116	3	2·6%	102	1	0·9%
1941	104	—	—	90	—	—
1942	143	1	0·7%	117	—	—
1943	139	2	1·4%	154	2	1·3%
1944	106	—	—	131	2	1·5%
1945	102	1	0·9%	141	3	2·1%
14 years	1,779	26	1·5%	2,105	29	1·4%

Analysis of Causes of Death

	Total	Subtotal
Pulmonary embolism	6	8
Respiratory infection	1	3
Cardiac failure (and C.V.S.)	5	2
Peritonitis (+ paralytic ileus)	7	2
Hæmorrhage	1	3
Other causes	6	11

The position as regards total *versus* subtotal hysterectomy has crystallized sufficiently to draw the following conclusions:

(1) Every patient with a benign condition requiring hysterectomy should have her cervix inspected prior to operation, if necessary under anæsthesia.

(2) Parous women and nulliparous women with unhealthy cervices should have the total operation.

(3) Lack of experience on the part of the operator should not be considered an indication for the relatively easier subtotal operation. It is essential for gynæcology that any surgeon opening the abdomen with a view to hysterectomy should be able to do a total hysterectomy as confidently and safely as he would do a subtotal hysterectomy.

(4) In a few cases of endometriosis and pelvic infection, a subtotal hysterectomy will have to be performed owing to the technical difficulties of a total operation. It should, however, be remembered that such cases are often those in which the total operation is most desirable, owing to the diseased nature of the cervix and the necessity for pelvic drainage.

(5) A subtotal operation is justified for a benign condition, provided the cervix is shown to be perfectly healthy, and the cavity of the uterus is either explored with a curette from below, or opened before the patient's abdomen is closed.

(6) Finally, if the conclusions I have drawn are accepted, more total hysterectomies should and will be done.

Mr. Clifford White: *Vaginal hysterectomy*; Mr. Gwillim has said that the ovaries are not always removable during vaginal hysterectomy; if so, this is not a suitable operation for carcinoma of the body of the uterus and should be given up in such cases. Plastic surgery to the ovaries is very difficult or impossible and appendectomy impossible. The results are better in the second hundred cases than in the first hundred and so it is not an operation for a surgeon to start performing if he is only likely to do one or two each year. Its advantages are: it gives practice for the combined hysterectomy and pelvic floor repair operation. It avoids irradiation of the ovaries in cases of menorrhagia. It ends pregnancy and sterilizes the patient in incurable thoracic disease associated with early pregnancy without the pain of coughing with a recent abdominal scar.

Subtotal hysterectomy is slightly quicker but this is only on rare occasions important to the patient, i.e. when anæsthetic difficulties occur unexpectedly. The saving of the surgeon's time because he has a long list of operations to perform is no reason whatever for performing the less efficient operation; he should give up some of his beds to his juniors. It is useful when the rectum is severely adherent. It avoids the troublesome oozing from the vaginal vault after cæsarean hysterectomy. After bilateral salpingo-oophorectomy to obtain a stump which is more easy to cover satisfactorily with peritoneum. In Mr. Kimbell's series he found that of 80 patients on whom Mr. White performed subtotal hysterectomy no less than 66 were cases of salpingo-oophoritis.

Total hysterectomy was, in Mr. White's opinion, undoubtedly the better operation to perform as a routine in straightforward cases of fibroids, &c. For one thing it gave the operator practice so that he was not afraid to undertake a difficult case of carcinoma of the body and it avoided stump carcinoma which was a grave danger even in nulliparæ, as Meigs, Cosbie and others had pointed out.

Mr. V. B. Green-Armytage: Vaginal hysterectomy is easy, safe, quick and accompanied by less shock, hæmorrhage, morbidity or mortality than that by the abdominal route.

Using the technique and principles which I described in 1939 (*Journal of Obstetrics and Gynæcology of the British Empire*, **46,** 848), 85% of my consecutive series of 981 cases were done for hæmorrhagic states, for I am adverse to the use of radium with its subsequent disorders.

In that series there were 8 deaths, a mortality of 0·8%. No death has occurred in the last 310 operations.

Indications for operation.

85% of operations were performed for hæmorrhagic metropathia, adenomyosis, fibromata, polypi or post-menopausal bleeding. 10% were for prolapse and morbid conditions of the cervix.

Complications.

There were 4 cases of secondary hæmorrhage, two of which necessitated laparotomy; 2 cases of obstruction due to a loop of small intestine becoming adherent to the floor of the pelvis; 2 cases of femoral thrombophlebitis; 3 cases of infected pelvic hæmatoma drained *per vaginam*; 1 bladder injury with immediate suture. No case of ureteric or rectal injury occurred.

Deaths.

1 died of acute dilatation of the stomach proved post-mortem; 2 died of tympanitic ileus without any evidence of inflammation or obstruction at post-mortem; 2 died of acute peritonitis and septicæmia; 1 died of embolism; 2 died of bronchopneumonia.

The technique described is anatomical and almost bloodless [as was demonstrated by the coloured film shown at the meeting]. The most important points I wish to stress are:

(1) the method of pushing the ureters back and laterally before opening the utero-vesical fold.

(2) the fact that every ligature overlaps its predecessor and each ligature is retightened after cutting the artery, i.e. on an empty vessel.

(3) that a proper bridge prevents cystocele or vault prolapse.

(4) that the patient is put back to bed with the foot of the bed raised 8 inches, and a self-retaining catheter in the bladder for forty-eight hours.

Finally I wish to protest against the anachronism of using clamps in 1950. Doyen used them in 1906. They predispose to embolism, infection and vault prolapse.

Mr. W. McKim H. McCullagh: After a panhysterectomy operation on multiparæ there is a danger of a high enterocele and of an increase in the prolapse of the vaginal walls, notwithstanding the tying of the round ligaments to the angles of the vagina. I prefer the total operation. In the Samaritan Hospital, in the period under review by Mr. Kimbell, I performed 284 abdominal hysterectomies, of which 255 or 90% were total hysterectomies, with a mortality of 4 or 1·5% for the total operation; two of these were cancerous. For the past few years I have made it a practice to unite the round ligaments, the utero-sacral ligaments, and the mid-posterior vaginal wall, in one coherent stump, by sutures. As a result the vagina is pulled back and up and lengthened. Thus a subsequent colporrhaphy, when required, is more easily and successfully performed.

Mr. Aleck Bourne: The crude statistics of the mortality rates of total and subtotal hysterectomy are misleading as a guide to the choice of operation. The deaths following subtotal hysterectomy are partly due to shock and hæmorrhage caused by a difficult operation where the originally planned total hysterectomy was impossible to complete.

A true comparison would be the mortality of the planned subtotal operation with that of all cases of total hysterectomy. A further fallacy is the aggregation of all types of patient in our crude mortality figure. Every woman is different in such details as age, anæmia, weight, capacity to withstand an abdominal operation, blood pressure, and many other factors which influence the ultimate result.

I can see no disadvantage to the patient in leaving a healthy, nulliparous cervix as I am not convinced that the incidence of carcinoma in the nulliparous uninfected cervical stump is higher after subtotal hysterectomy than in the nullipara who has not been subjected to subtotal hysterectomy. Further there are advantages to the patient in leaving the cervix, inasmuch as the subtotal operation is quicker, it does not disturb the supports of the vaginal vault, and the cervix plays some part in a woman's sexual life.

Mr. John Stallworthy: There are at least three ways of performing a hysterectomy and no gynæcologist is properly equipped until he has mastered the technique of both the vaginal and the abdominal hysterectomy. There has been a tendency in the past for certain schools to develop one technique to the exclusion of the other. The bias towards abdominal hysterectomy is well shown in the Chelsea figures and, at least until the last war, the bias towards vaginal hysterectomy was well demonstrated in Vienna. The decision as to when to perform a vaginal removal of the uterus and when to remove it by the abdominal route does not matter as long as the basic fact is accepted that each technique has its place.

I agree that there is little place for subtotal hysterectomy and in my own Department nearly 94% of all hysterectomies consisted of total removal of the uterus by either the abdominal or the vaginal route; the latter was used in approximately 20% in the last 2,000 cases.

Mr. W. Hawksworth: Details of the last 2,054 hysterectomies performed in the Area Department of Obstetrics and Gynæcology at the Radcliffe Infirmary, Oxford, were presented so that comparisons could be made with the figures already presented by previous speakers, and also so that they could be placed on record as work done in one of the younger Departments outside the London area. The figures would then be available should anyone ever collate the records of hysterectomies done throughout the country.

The figures presented were:

Total abdominal hysterectomies	1,171
Percentage of all hysterectomies performed	57·01%
No. of deaths	14
Mortality	1·19%

Of the 14 deaths, 5 followed total hysterectomy for carcinoma of the body of the uterus. The mortality is higher for patients in this group in that they are older and poorer risks surgically.

The mortality must depend upon the number of patients operated upon out of the number seen. In a review recently carried out of 104 cases of carcinoma of the body of the uterus operated upon in the Area Department, the operability rate was 91%.

Subtotal hysterectomy	507
Percentage of all hysterectomies performed	24·19%
No. of deaths	2
Mortality	0·4%
Vaginal hysterectomy	380
Percentage of all hysterectomies performed	18·8%
No. of deaths	0
Mortality	0%

The figures for the last two years were as follows:

Total hysterectomy	340
Percentage of all hysterectomies performed	68·51%
Subtotal hysterectomy	46
Percentage of all hysterectomies performed	9·32%
Vaginal hysterectomy	110
Percentage of all hysterectomies performed	22·17%

It will be seen from these latter figures that when a hysterectomy is performed in this Department that it is a total hysterectomy, either by the abdominal or vaginal route in over 90% of cases.

The speaker had no doubt in his own mind that it was in the best interests of patients that a total hysterectomy should be performed in preference to a subtotal hysterectomy wherever possible.

He asked if information could be given on the subject of enterocœle, following vaginal hysterectomy. He felt quite sure that all people who performed vaginal hysterectomies did come across this complication. He had recently attended a meeting of the Birmingham and Midland Obstetrical Society and at that meeting a series of 100 cases were presented by the Obstetrical and Gynæcological Registrar of the United Birmingham Hospitals and the recurrence rate of enterocœle was as high as 11%.

Dr. Edith Hall: The method of hysterectomy by conization of the cervix is an operation which I have practised for many years in selected cases, particularly in those multiparous patients with lax vaginal walls, but no definite prolapse, who might later develop vault prolapse as a result of heavy domestic work. I do not agree that panhysterectomy is never followed by vault prolapse.

Conization produces a firm vaginal vault and it is possible to remove the whole of the vaginal cervix as well as the cervical canal, so that there is no risk of the development of cervical carcinoma, nor is the risk of secondary hæmorrhage increased in my experience.

Mr. Derek Freeth: I use No. 3 plain catgut instead of chromic catgut for ligaturing all pedicles. Plain catgut does not snap like chromic catgut sometimes does, is more supple and easier to use. No. 3 plain catgut lasts sufficiently long for thrombosis to occur in large vessels and as it is more readily absorbed, there is less tissue reaction with, consequently, a lower post-operative morbidity.

Section of Epidemiology and State Medicine

President—W. H. BRADLEY, D.M., M.R.C.P.

[*May* 19, 1950]

The Mechanism and Prevention of the Rheumatic State

PRESIDENT'S ADDRESS

By W. H. BRADLEY, D.M., M.R.C.P.

I MAKE no apology for using the term "the rheumatic state". This was Cheadle's choice in his important lecture of 1889; in the present context it allows me to discuss not only acute rheumatism but also some forms of arthritis of the rheumatoid type which I shall not always differentiate in the text.

In the years immediately following World War I there was plenty of acute rheumatism to see. The Aschoff body was known to be the specific and characteristic lesion. The cause of the granuloma was unknown, but Poynton and Payne in 1913 had produced similar lesions by infecting rabbits with what they called "the *Diplococcus rheumaticus*". What this streptococcus was we do not know. Ten years ago I asked Poynton if there was a strain of it surviving, but all strains had been lost. Although the idea that a streptococcus, or rather an infective factor, might in some way be involved was mentioned by my teachers it did not seem to be a matter of any great importance. At that time the implication made little impression on me, and I am fairly certain that the same can be said of most students then and now during the period of clinical training. As late as 1948 John Ryle wrote: "With ætiology—the first essential for prevention—and with prevention itself the majority of physicians and surgeons had curiously little concern."

Neither did my teachers draw any inference from Sir Arthur Newsholme's lectures of 1895, demonstrating an endemic prevalence of acute rheumatism with irregular periodicity in this country. Because acute rheumatism could not be looked upon as a communicable disease in the ordinary sense of the word, the knowledge that an infective factor probably existed appeared to be of little practical importance to the cardiologists and pathologists who taught me. I doubt if the position has changed much since, although some teachers now give a clear message. For instance, John Ryle, whose untimely death this year we still lament, had certainly become convinced of the role of the factor of infection (Ryle, 1948), and John Parkinson, perhaps the greatest contemporary teacher on the subject, stated (1945) that in his personal opinion "streptococcal infection has some causal relation with rheumatic fever"; but these are, I believe, exceptions, and we see little sign of any attempt to do much about the infective aspect.

It was not until I found myself caring for a public school for boys and called upon to scrutinize applications for entry and to make routine examinations when the boys joined the school that I began to look especially for a history of rheumatism or signs of earlier endocarditis and tried to keep such boys out of the school or to restrict their activities. Then, twenty-five years ago, I preferred boys without tonsils, which was in keeping with the current teaching, but I did not give the matter serious thought until Dr. J. A. Glover addressed this Section in 1928. After a couple of years as school doctor I had realized that my main problem was going to be a succession of waves of acute nasopharyngitis. As far as I could see, the sore throats, the feverish colds and the "flu" fell equally upon the boys with tonsils and the tonsillectomized, and I began to work out the incidence of upper respiratory infection in relation to the presence or absence of tonsils or the history of operation. I bought myself a nice new tongue depressor with a light on the end. By memorizing the size of a 1 cm. cube of wood, I was able to estimate the weight of lymphoid tissue in the throat and neck, and

now I was all set, harnessed to a technique and anxious to examine, generally twice daily, every boy in the school who was in any way unwell. The effort was worth while for two reasons, firstly the B.M.A. gave me the Charles Hastings Prize (Bradley, 1930) for the simple little sums I did to satisfy myself that tonsillectomy did not alter the incidence of acute upper respiratory infections, and secondly, it brought me into close touch with Dr. Glover, who has been a source of inspiration to so many members of this Section through the long years he has served it. Glover involved me in the Medical Research Council's "Epidemics in Schools" inquiry and he arranged for me to send throat swabs to Dr. F. Griffith (1934) whenever I thought a new streptococcus was active in the school. I had an idea that different strains of *Streptococcus pyogenes* might produce a slight but nevertheless distinguishable variation in the appearance of the exudate on the tonsil (Bradley, 1939*a*). This may sound fantastic, but I was able repeatedly to hint to Griffith that something new in the way of streptococcal infection had appeared in the school, whereupon he would immunize a rabbit with the new strain. As the result of this, new types were added to the Griffith classification on three occasions, and, in all, six different Griffith types of *Streptococcus pyogenes* caused outbreaks in this school during six years (Bradley, 1938).

The "Precursor Fever" in Rheumatism

I was getting into my stride on these observations on sore throats when *Streptococcus pyogenes* type 13 appeared in the school, and in due course acute rheumatism followed in some boys who had already had sore throats. The pattern of sore throat, three weeks' lag period and then acute rheumatism was faithfully reproduced. In all, 29 attacks of rheumatism were observed in this school of 340 boys between May 1929 and April 1931 (Bradley, 1932). The disease occurred during two terms in each of which a different Griffith type of streptococcus was involved in producing the sore throat preceding the rheumatism. The sequence of rheumatism following sore throat was an old story: Lesague and other French writers had insisted upon it years previously; one of the best descriptions was written by Haig-Brown, Medical Officer to Charterhouse School in 1884, and Glover had already published his 1930 *Lancet* paper mentioning two small epidemics of rheumatism in schools. The outbreak I had witnessed, however, was the first in which there was continuous observation both bacteriologically and clinically: it gave a fine lead on the nature of the "rheumatic tonsil" as it was then called, particularly as the "epidemic sore throat" was due to two distinct types of group A *Streptococcus pyogenes*.

This did not mean that all "rheumatic tonsils" were due to group A streptococcus but it did mean that the sore throat preceding rheumatism in my series was the acute communicable disease which sometimes produced the clinical picture of scarlet fever. Chronic tonsillar sepsis did not come into the picture. The matter, particularly the epidemiology of the acute streptococcal sore throat, appeared to be worth further study. There were others in this country who thought the same, and in America Coburn (1931) was producing an interesting monograph on the subject.

The Hereditary Factor in Acute Rheumatism

Although I saw other outbreaks of streptococcal fever in the school, none of them was associated with rheumatism. However, an occasional case of acute rheumatism occurred in my general practice, notably in one family. Ben Jones and his wife had 21 children, 15 of whom were surviving when Mrs. Jones died at the age of 53 of mitral stenosis. 5 of the family were in my care, 2 of them with rheumatic heart disease and one with arthritis of the rheumatoid type. There was a history of rheumatic fever in others and I treated one grandchild with acute rheumatism. Unfortunately I was unable to trace all the ramifications of this family, but it was, in fact, very similar to that recorded by Pickles (1943) in Aysgarth. (Fig. 1.)

This genealogy, representing that 23 out of 53 of the descendants of one man had rheumatic fever or carditis brings to life the calculations of Gould *et al.* (1938, 1939) and Wilson and Schweitzer (1937) who stated, as a natural law, that the predisposition to acute rheumatism was a mendelian factor with a recessive autosomal transmission. It may be significant that amongst the 25 boys involved in the school outbreak there were two brothers.

The Factor of Infection in Rheumatism

To return to my reminiscences and the infective factor: In 1933 the school divided, the junior boys being removed elsewhere. The reduction in the size of the school community at risk was followed by a surprising reduction in the incidence of upper respiratory disease. Streptococci disappeared as an epidemic entity. Naturally I ascribed this to improved spacing, but I am now less certain because at about this time the demise of streptococcal disease had begun.

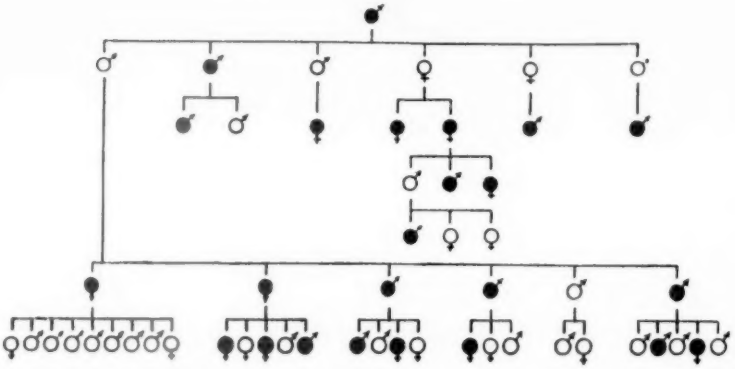


FIG. 1.—The "Alan of Brittany" family (spouses omitted). Pickles, W. N. (1943) *Lancet* (ii), 241. Black circles indicate members of the family with a history of rheumatic fever or signs of mitral stenosis.

In 1936 a Rockefeller Fellowship took me to America to work with Alvin Coburn and in nine busy months I managed a field survey of streptococcal disease in the homes of acute rheumatics in New York City (Bradley, 1937). I was able to observe repeatedly the spread of *Streptococcus pyogenes* through rheumatic families. The sequence of acute streptococcal sore throat, a lag period of about a fortnight and then the first attack or relapse of acute rheumatism, was sufficiently predictable, about a 1 in 4 chance in those days, to make it worth while studying the antibody response and other blood changes from the beginning of the sore throat. The pattern of antibody response was constant and no less characteristic than is the response to other antigens causing acute communicable disease, e.g. typhoid or diphtheria. A rise in anti-streptolysin "O" was always present in the large series of cases of active rheumatic fever which Coburn and myself (Eagles and Bradley 1939) studied. This demonstration was made possible by the work of Edgar Todd (1938), then Assistant Director at the L.C.C. Serum Laboratory at Belmont, Surrey, who isolated and described the two streptolysin fractions.

Okell's (1932) unitarian hypothesis, asserting that the manifestations of streptococcal infection were numerous and that scarlet fever was one of them, was gaining acceptance and agreed with Griffith's experience. There was at this time an abundance of cases of scarlet fever in New York and I was given a free run of the scarlet fever wards at Willard Parker Hospital. I was satisfied that for all practical purposes scarlatinal rheumatism and rheumatic fever were identical diseases.

ANÆMIA IN ACUTE RHEUMATISM

One of the things about these cases of scarlet fever which struck me forcibly was the occurrence in some of pallor and a rise in blood sedimentation rates, without polyarthritis and sometimes without much fever, at the time when rheumatic attack or relapse was to be expected. To me the pallor was the striking feature in these incidents which as they increased in severity graded into the more common picture of acute rheumatism. On my return to England I joined John Ryle when he set up his Department of Medicine at Cambridge and began to study this pallor, thinking it might have a bearing on the mechanism of the rheumatic attack. From daily examinations of the blood following acute streptococcal sore throat in rheumatic persons I found that the rise in blood sedimentation rates which heralded the rheumatic attack and persisted during rheumatic activity was so closely paralleled by the packed cell volume that the two were intimately related. With the help of Dr. Gertrude Plout I found that this apparent anæmia was not associated with consistent reticulocyte response or other signs of red cell regeneration and concluded that in all probability the anæmia in acute rheumatism was a dilution phenomenon; others (Hubbard and McKee, 1939) have explained similar findings by suggesting that there is a cessation of erythropoiesis during rheumatic activity. To settle this question I made with Drs. G. Hadley, A. C. E. Cole and Elvira De Lie, serial blood volume studies using Congo red and Evan's blue dye methods. Although the reliability of these blood volume techniques may be in doubt, our findings, repeated every two or three days, were fully consistent with the idea that the anæmia of acute rheumatism is essentially due to an absolute increase in the circulating plasma volume (Bradley, 1939*b*), and not to red cell destruction.

TABLE I.—TOTAL SERUM PROTEINS COMPUTED FROM SERUM DENSITY

	Serum Density (In g./ml. at 20° C. Method—Barbour, H. G., and Hamilton, W. F.)				Computed Serum Proteins (*Factors*: Density of non-protein fraction 1·0076 (Kegan); Density increment per gramme of protein 0·0026 (Adair))			
	No. of patients	Range	No. of samples	Range of averages	Average	Average gm. %	Number of patients in whom was observed— Hyperproteinæmia (S.G.>1·0284)	Hypoproteinæmia (S.G.<1·0236)
Acute rheumatism								
Active	25	1·0236–1·0320	128	1·0249–1·0319	1·02678	7·37	9	—
Recovering (ESR 20/100)	10	1·0237–1·0306	34	1·0237–1·0275	1·02583	7·02	1	—
Recovered	10	1·0231–1·0276	18	1·0237–1·0267	1·02525	6·79	—	1
Rheumatoid								
Active	2	1·0254–1·0339	25	1·0286–1·0288	1·02870	8·10	2	—
Moderately active	6	1·0242–1·0274	9	1·0245–1·0274	1·02608	7·10	—	—
Burnt out	8	1·0228–1·0263	18	1·0232–1·0263	1·02450	6·50	—	3
Gout	1	1·0254–1·0269	4	1·0259	1·02590	7·04	—	—
Para-rheumatic								
Erythema nodosum	3	1·0251–1·0282	8	1·0251–1·0280	1·02623	7·17	—	—
Chorea	3	1·0249–1·0279	8	1·0257–1·0262	1·02600	7·08	—	—
Acute nephritis	1	1·0270–1·0290	3	1·0279	1·02790	7·80	1	—
Various acute infections	28	1·0212–1·0296	56	1·0225–1·0289	1·02496	6·68	1	5
Subacute bacterial endocarditis	4	1·0215–1·0268	11	1·0223–1·0240	1·02335	6·05	—	3
Diseases of liver parenchyma	9	1·0214–1·0259	11	1·0214–1·0251	1·02350	6·07	—	5
Hæmorrhage with dilution	5	1·0190–1·0236	11	1·0200–1·0236	1·02196	5·51	—	4
Healthy young adults	18	1·0223–1·0279	18	1·0223–1·0279	1·02456	6·61	—	—
Totals	133	1·0190–1·0339	362	1·0200–1·0309	1·02544	6·87		

By this time it was already widely known that the characteristic change in the serum of rheumatic patients was a reduction or even a reversal of the albumin-globulin ratio with normal or increased total protein except under special circumstances. Such changes are not specific for the rheumatic state but occur in many infections. Daily examination of serum proteins by chemical means in a large number of patients with acute rheumatism is not easily obtained. I, therefore, applied serum specific gravity determination to the problem and was surprised in view of the dilution phenomenon to find that specific gravity was above normal throughout the period of rheumatic activity. Table I compares acute rheumatism with some other diseases in this respect.

In the rheumatic patients the serum is pale in colour and deficient in bile pigments yet there is hyperproteinæmia. In the conditions produced by hæmorrhage the serum is also pale, but blood dilution is accompanied by a reduction in plasma protein per unit volume.

One important point in connexion with Table I is the serum specific gravity in hepatitis and other diseases involving the liver parenchyma. The comparison with the rheumatic states may be of vital importance regarding the mechanism of the antagonism between hepatitis and rheumatism and I shall mention it again later.

The presence of a high specific gravity, which is equivalent to a high serum protein content of the serum, combined with the increase in blood volume, implied an unexpectedly great increase in the total circulating protein. This hyperglobulinæmia was a constant abnormality and significantly above the levels in the acute infections studied. Given the plasma volume and the plasma protein per unit volume it is possible to compute the amount of circulating protein. From such calculations, assisted by Drs. McCance and Widdowson, I found that sometimes more than twice the normal circulating globulin was present during active rheumatism and that the total circulating albumin tended to be somewhat below normal during activity. The fibrinogen was unstable. Such findings would be unusual except in a hyperimmunized animal. The qualitative change associated with the production of large quantities of globulin is splendidly illustrated by electrophoretic and high-speed centrifuge analysis. Fig. 2 was provided by Drs. A. S. McFarlane and A. Kekwick of the Lister Institute who investigated serum from several of my patients and obtained consistent results. Similarly the quantitative results were consistent: the total circulating proteins being at a high level during the height of the rheumatic activity and falling as the disease became quiescent. Robinson (1943) has since confirmed these observations in rheumatoid arthritis and has coined the phrase "hydræmic syndrome" to describe the phenomenon.

If rheumatism itself is an infective condition and the globulin mobilization is the antibody response to a specific rheumatic infection, one would expect antibody production to increase and persist into convalescence and to appear as a reciprocal of the disease process. This is not the case in acute rheumatism; the rise precedes the onset of rheumatism and runs parallel with its course. Furthermore, the quantity of antibody globulin mobilized is much greater than is required to deal with the suppurative and erythrogenic manifestations of streptococcal infection. In face of the conviction that *Streptococcus pyogenes* initiates the rheumatic process and in view of the demonstration that part at least of the antibody globulin mobilization was accounted for by anti-streptolysin, I concluded that the high globulin level was not merely an effect but might play a direct causal role in the mechanism of rheumatism.

A Complex Mechanism

In my attempts to understand the mechanism of the rheumatic state the whole of my experience has led me to the idea that the antibody response, not in the sense of an allergic reaction but in terms of milligrammes of protein, normal or abnormal, plays a very important part. The position might be stated as follows. Acute *Streptococcus pyogenes* infection (and I do not exclude the possibility of certain other infections) fires off a chain of events. The characteristic streptococcal disease then ceases to bother the patient *qua* infection and the lag period follows. By the time the rheumatic process is active the streptococcal infection is no more than a remote cause and a new factor, almost certainly involving an inherited predisposition, has emerged as a continuing cause of the rheumatic state (including some forms of "rheumatoid arthritis" as well as the acute "juvenile" rheumatism). I postulate an excess of antibody globulin, normal or abnormal, as this cause. If this is so McFarlane's electrophoretic studies failed to pick out a separate and peculiar globulin fraction, so that there is, so far, no reason to believe that the globulins in rheumatism are qualitatively abnormal although they still may be shown to be so. I feel certain that they are abnormal quantitatively and less innocent and beneficial than might at first be supposed. The crucial test appears to be plasmaphoresis or substitution transfusion and I still hope someone will try the latter, which is now fairly practicable.

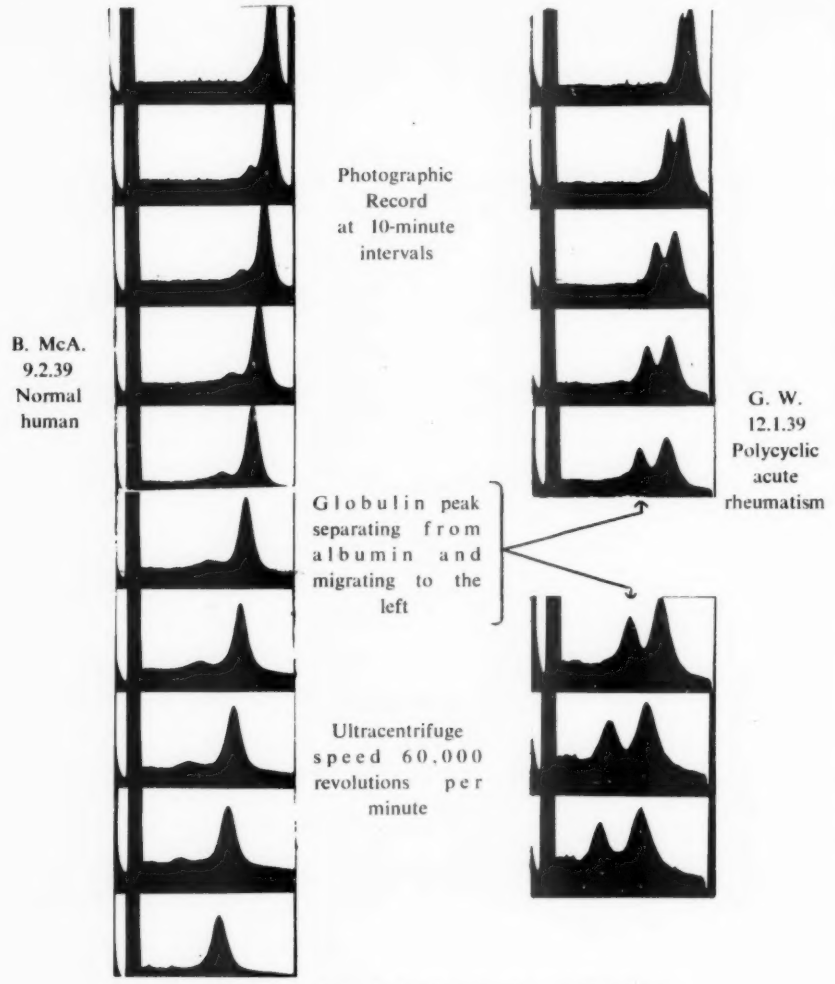


FIG. 2.—Movement of protein fractions in ultracentrifuged serum.

"DIVERSIONS"

I made several abortive attempts to get beyond this point but was troubled by certain other time-consuming diversions, for example Schlesinger's (1935) elementary-body theory and Sabin's (1939) pleuropneumonia theory. With regard to the former, Eagles and myself (1939) examined serum from 54 patients and found that the Amies reaction was non-specific. The agglutination of so-called rheumatic elementary bodies was elicited equally well by serum from patients with rheumatic fever, arthritis of the rheumatoid type and arthropathies not classified as true rheumatism. With regard to the Sabin theory, Sir John Ledingham, who was one of my supervisors, had for many years been interested in a pleuropneumonia-like organism. Using material provided from my cases Dr. E. Kleineberger and Sir John Ledingham were unable to recover the organism postulated by Sabin as being associated with rheumatism (Bradley, 1942).

When I had done this work war was imminent. The Ministry of Health wanted an epidemiologist and took me on. At the Ministry one of my first tasks was hepatitis, and when

this presented itself as a major military problem I found myself on the M.R.C. Jaundice Committee.

Antagonism between Hepatitis and Rheumatism

I have already described to this Section (Bradley, 1946*b*) some of the work on hepatitis which included an attempt to transmit epidemic hepatitis and homologous serum jaundice to patients suffering from intractable rheumatoid arthritis. My readiness to co-operate with Dr. MacCallum (1944) arose largely from my interest in the mechanism of rheumatism.

The details of the effects of hepatitis on rheumatism still await publication but in a few women the results were for a time dramatic, and were sufficient to convince me that experimentally produced virus hepatitis can suddenly halt or reverse the mechanism of rheumatism. It was from a similar point that Hench and his colleagues started on the search which led to cortisone. I should like, however, to remark that the experience we had at St. Stephen's Hospital in 1944 was unique, because we were able to anticipate the hepatitis and to watch its development in the rheumatoid. Amelioration of the rheumatic symptoms occurred in some cases during the pre-icteric phase and before jaundice was apparent. I have stated elsewhere (Bradley, 1946*a*) that a study of the histology of the liver of fatal cases of homologous serum jaundice suggests that hepatic necrosis is a sudden event, probably preceding the onset of symptoms, and I obtained the impression that the relief of rheumatism has nothing to do with icterus but occurs when the liver function is at its lowest ebb in the initial stage of hepatitis. Table I shows that low serum proteins are characteristic of acute hepatitis and some other diseases of the liver parenchyma. I feel that this may well be the clue to the remarkable antagonism between hepatitis and rheumatism.

Recent Developments—Cortisone

Hench has said that the effect of cortisone closely resembles the effect of hepatitis in rheumatoid arthritis. When considering the mechanism of the rheumatic state it would be well to imagine that both these "cures" are brought about in the same way. In this connexion, I suggest, we should examine the hypothesis that, in the cure of the rheumatic state, cortisone works through its function as an "S" hormone affecting the conversion of protein into glycogen. I should expect a collagenolytic effect to be more important than any influence on the production of γ globulin by lymphoid tissue and cells.

Perhaps I should elaborate this mention of collagen. I am in sympathy with those pathologists who include the rheumatic state in the group of diseases affecting the mesenchymal tissues and who consider collagenization—the diffusion of a hyaline ground substance—as the fundamental pathological change preceding the formation of the characteristic granulomata. In this connexion I think there may be a close analogy between the rheumatic state and amyloidosis. It is not unreasonable to suggest that if one could dispel the amyloid substance in lardaceous disease one would cure the disease. Similarly in the rheumatic state, if one could dispel the collagen one might cure the rheumatism, and I suspect that the collagen deposits, which are not antigenic in the serological sense (Wakeman, 1949), are in some very simple manner related to the high protein content in rheumatic blood. While I was using Congo red for blood volume studies one patient with acute rheumatism came to autopsy. He was not suffering from clinically recognizable amyloid disease and had been ill for a few days only, yet at autopsy the red dye was found fixed in his joint capsules and other connective tissue elements. Goldthwaite (1940) has observed that 21 % of his cases of rheumatoid arthritis examined at autopsy had evidence of "amyloidosis".

Whether these amyloid-like deposits can be dispelled by cortisone might be measured by the liberation of a fixed dye.

The Mayo Clinic workers have emphasized that A.C.T.H. and cortisone must, for the time being, be regarded as research tools and not as a practical therapy of the rheumatic diseases. It would indeed be absurd for us to sit back and wait until there is sufficient of them to treat the millions of cases of rheumatism which we know must always exceed the available supply of cortisone: I suggest that an important line of enquiry should be to discover what influence the glands of internal secretion have upon the production of antibody globulin; and more important, its disposal in the rheumatic subject and the non-rheumatic person.

The Remote and the Continuing Causes of Rheumatism

I notice with interest that the very informative report of the Scientific Advisory Committee of the Empire Rheumatism Council on a Controlled Investigation into the Ætiology and Clinical Features of Rheumatoid Arthritis (1950) subscribed to the idea that the rheumatic state is associated with the "general adaptation syndrome" postulated by Hans Selye (1949).

Personally I should hesitate to consider, in relation to the amelioration of rheumatoid arthritis, hepatitis as an "alarm stimulus" or to attempt to explain its influence on a non-specific hypothesis. Similarly, to me the factor of infection in the rheumatic state—that is the remote cause—and the inherited factor, are very specific things and I think it may well be found that the continuing cause—that is the inherited factor—is a hormone defect impeding glycogenization of an excess of globulin—it may be in the tissues as well as in the blood stream.

Prevention of Acute Rheumatism

Quite apart from whether this guess is a good or bad one, I feel strongly that we, as epidemiologists, must not allow the factor of infection to be forgotten, neither must we allow the hope of a practicable therapy to put out of our minds the possibility of a more radical attack upon the mechanism of rheumatic disease and its prevention.

The remarkable decline in the incidence of streptoccocal disease in recent years, which has less to do with antibiotics and chemotherapeutic agents than one might imagine, may not continue indefinitely. Perhaps the upward swing in the curve of notifications of scarlet fever during the past winter is the first hint of the beginning of a new cycle of streptococcal disease and acute rheumatism. The decline in rheumatism has obviously had nothing to do with the inherited factor: the queer quirk put right temporarily by cortisone. It is inconceivable that this decline has resulted from a process of natural selection which would act by breeding out the rheumatic persons from the race in the course of a couple of generations. All the data that we have been able to assemble points to the factor of infection as the variable which has ceased to operate as vigorously as thirty years ago. The epidemiologist knows from long experience that unexplained trends in the incidence of communicable disease have a way of reproducing themselves cyclically. If we hurry now, we may be able to steal a march on the streptococcus and influence the incidence of rheumatic heart disease which, I understand, is already on the rise in some districts.

I believe there are four key points in the situation:

Firstly, a considerable proportion of persons genetically predisposed to rheumatism can be detected on the basis of family history.

Secondly, chemotherapeutic and antibiotic agents, although valueless in the treatment of the rheumatic state, have been applied successfully in the prevention of relapse.

Thirdly, it is not impracticable to attempt to protect genetically predisposed individuals from contact with *Streptococcus pyogenes* and to use chemoprophylaxis.

Fourthly, restriction of size of rheumatic families will, by improving the economic state of the individual child, tend to increase the probability of survival of existing members of the family.

I have thought carefully about this plan and no longer have any hesitation in commending it to the Medical Officers of Health who have the facilities to bring rheumatic families under review, particularly those working in the areas where acute rheumatism is notifiable; and to the local Health Authorities, whose powers under Section 28 of the National Health Service Act, 1946, might now be brought to bear on this subject.

Broadly speaking, the children of rheumatic parents should be under the observation of Public Health Officers. They should be as far as is practicable housed in single bedrooms, employed in the fresh air and in small communities, nourished adequately, adapted to chemoprophylaxis which should be applied at selected seasons, and educated to protect themselves from upper respiratory infection. They should be advised never to marry a rheumatic subject and to restrict their own families so as to be able to provide each child with a protected environment. Some of them might migrate to non-rheumatic zones in the world.

On the point of chemoprophylaxis of rheumatic fever I can continue my reminiscences. In April 1943 Sir Edward Mellanby called a conference to discuss research into acute rheumatism which advised an enquiry into chemoprophylaxis. A Sub-committee presided over by Professor Ryle has reported to the M.R.C., but the report was not published because after two years' enquiry it was felt that some of the records were untrustworthy and because much of the work was disrupted by the flying bombs. The results in themselves were not worth comment but the investigation did not disprove American claims that chemoprophylaxis of acute rheumatism is effective; in fact, there was something in the information obtained by the enquiry which suggested that the investigation should be continued. The real difficulties were that the conditions of observation were unsatisfactory and the incidence of acute rheumatism low at the time. This enquiry taught me one great lesson. One cannot farm out research; those responsible must be intimately and constantly engaged in the actual work.

With regard to prevention, someone is sure to say "we must wait until Koch's postulates are satisfied and *Streptococcus pyogenes* proved to be the main inciting cause in acute rheumatism". I hope that what I have said will show that this may be impossible. The concept of the remote and the continuing causes being separate and yet essential to the mechanism of the disease envisages a situation foreign to Koch. The gravity of the rheumatic problem justifies heroic therapeutic and experimental procedures: it also demands a bold attitude of mind which dares to take risks with academic concepts. Even if the responsibility of *Streptococcus pyogenes* is doubted, the overwhelming probability of a factor of infection is undeniable and the epidemiologists have provided the main evidence. The factor of infection is clearly a very common one, endemic in the rheumatic zones, and occurring locally in epidemics. This infection may attack the same individual repeatedly during the course of his life. Paradoxically, it is effective because the patient is hyperimmunized. It is a factor influenced by overcrowding and unhygienic conditions: it is a factor exhibiting remarkable epidemiological trends in incidence.

No matter what its real nature may be, the factor of infection in rheumatism is one to which we should apply the general principles of hygiene, and if we accept, as we must on all the evidence, that a factor of inheritance also exists we know where to concentrate our efforts in the prevention of acute rheumatism.

If we want a precedent we can reach back half a century to Newsholme (1895) who said much the same thing.

Summary

(1) Given a factor of inheritance with mendelian characters, and also a factor of infection by an agent particularly widespread in nature, we can speculate with some degree of safety that the mechanism of the rheumatic state depends on an abnormal response (inherited factor) to a specific antigen (infective factor). The inherited factor is not communicable (except genetically). The infective factor appears to be *Streptococcus pyogenes*—a very common infection.

(2) With less safety we can guess that the genetic abnormality resides in the physical characters of the antibody produced by persons genetically marked, or in the disposal of such antibodies by such persons.[1]

(3) At the beginning of the rheumatic attack, not during the precursor fever, there is a marked increase in circulating plasma volume, and also a significant increase in the specific gravity of the serum. From the very beginning of the rheumatic attack, antibody protein has already been mobilized, seemingly in response to a stimulus occurring days previously. Electrophoresis demonstrates that these changes are associated with a great excess of protein migrating with γ globulin. It is not known whether this protein is qualitatively unusual. If it is produced in response to an antigen operating initially at the time polyarthritis occurs, the magnitude and rapidity of the development of the immune globulin is unprecedented. This, therefore, is improbable.

(4) Chronologically the mobilization of globulin is intimately associated with the course of the disease. It is certainly not associated with "immunity" (that is freedom from) rheumatism.

(5) It is postulated that in genetically predisposed individuals streptococcal infections incite the production of a surfeit of normal or abnormal antibody protein. The signs and symptoms of the rheumatic state may be produced mechanically by the presence, in the circulation and interstitially, of excess quantities of globulin and a resulting increase in blood volume.

(6) Perhaps cortisone works by virtue of its "S" hormone effect whereby protein is converted into glycogen.

(7) Cortisone has a bearing only on the effect of the inherited factor in rheumatism. The infective factor remains as a problem which the hygienist can attack.

(8) The prevention of acute rheumatism is practicable with existing knowledge and facilities, and I believe the same applies to certain forms of arthritis of the rheumatoid type in adults.

[1]This concept is in keeping with the three phases in the natural history of a clinical case of acute rheumatism (Bradley, 1932). It is also supported by the histological evidence that, initially, the brunt of the rheumatic attack falls on the reticulo-endothelial system and that "collagenization", i.e. the diffusion of a hyaline substance, precedes cellular infiltration and the subsequent formation of the characteristic Aschoff lesion. Sections of early lesions in acute rheumatism suggest that a large quantity of protein has escaped into tissues which show negligible signs of other inflammatory reaction. This histological picture is present at the beginning of the rheumatic attack and may represent the basic pathological change.

I should like to exhort members of the Section to further effort in this direction by quoting from John Parkinson's Harveian Oration (1945): "Let us proceed in a fresh spirit of post-war dedication, and work in hope and confidence for the ultimate defeat of this the most deadly enemy of youth."

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Section of Radiology

President—S. COCHRANE SHANKS, M.D., F.R.C.P., F.F.R.

[*April* 21, 1950]

Radiology of the Infected Temporal Bone

By Sir HAROLD GRAHAM-HODGSON, K.C.V.O., F.R.C.P., F.F.R.

To the radiologist interested in the temporal bone, one of the most important requisites is a close co-operation between him and his otological colleague, for without that co-operation little, if any, progress can be made. Where such co-operation exists, the radiology of this bone is a most fascinating subject, as the anatomy is complicated, the pathology and ætiology to an appreciable extent unknown, the radiography intricate and the radiological interpretation difficult and often uncertain.

Usually, when we radiologists consider this part of the body, our thoughts fly to the mastoid process, but this is "putting the cart before the horse". Mastoiditis is not a disease entity in itself, but is a complication of otitis media which, in its turn, is in the great majority of cases a sequel to nasopharyngeal infection.

The first signs of infection present themselves clinically and radiologically in the eustachian tube and the middle ear and, finally, in the mastoid cells, infection of the latter being a sequel to the others.

It is logical, therefore, for the radiologist to study the path of infection and to concentrate first of all on the radiology of the middle ear and eustachian tube, finally considering any X-ray evidence of spread of infection to the mastoid process itself.

When considering the radiology of the temporal bone, it is important at the outset to appreciate its fundamental difference from the radiology of other parts of the skeleton, for in the temporal bone the surgeon primarily requires from the radiologist anatomical information as to the type of petro-mastoid he is dealing with, information which he cannot obtain by other means short of operation. It is only secondarily that he wishes to know whether there are or are not any X-ray signs of infection and, in many cases, the X-ray evidence is only corroborative of the obvious clinical signs and symptoms.

The necessity for this somewhat unusual radiological approach becomes apparent when one considers that the course which infection takes in otitis media is very largely dependent on the degree of pneumatization of the petro-mastoid bone. It has long been recognized that approximately 95% of cases of chronic otitis media occur in diploetic or poorly pneumatized mastoids, commonly called the "infantile type".

Acute otitis media may occur in connexion with either the infantile or adult type of mastoid, but a resulting acute mastoiditis is more prone to occur in the adult type, since diploetic bone is more resistant to infection than the well-pneumatized, freely connecting cells.

The border line between an adult and infantile type of mastoid was vague and difficult to define until Diamant's investigation of approximately a thousand persons, all over 10 years of age. About 40% had no symptoms of ear disease; the remaining 60% were suffering from acute or chronic otitis media. He took radiographs of the mastoid processes of these patients in the lateral oblique projection and measured the cell system by means of a planimeter. His investigation showed that the cell systems in adults normally vary from 0 to 30 sq. cm. with an average size of 12 to 13 sq. cm. The examination of patients with chronic otitis media showed that the average value of the air-cell system was 2·89 sq. cm.—a striking difference from the normal subject, 12·27 sq. cm. In other words, patients with chronic otitis media have, on an average, one-fourth as large an air-cell system as that of normal patients. In particular, it should be pointed out that in practically every case of Diamant's series suffering from chronic otitis, the size of the cell system falls far short of the average value for normal subject.

Diamant states that "if a cell system is found to exceed 16 sq. cm., one may assert that if

infection should occur, it will not give rise to a permanent change in the tympanic membrane". This means that the person will never have chronic otitis, according to Diamant, whatever form of treatment is adopted. This is a far-reaching statement and, if borne out by other investigators, one of very important prognostic value.

It is a remarkable fact that if the cell systems in a pair of mastoids are asymmetrical and the patient contracts a unilateral otitis media, it is invariably the ear with the smaller cell system that is affected.

Enough has been said to show how important is the bearing which pneumatization, or lack of pneumatization, has on the clinical course of the disease. It is also of very great significance in the radiological interpretation.

An early acute infection in a well-pneumatized mastoid is demonstrated with ease as any change in the radiolucency of the cells can be seen in such a case. But, though X-ray diagnosis of infection is comparatively simple in a cellular mastoid, the fewer cells that are present the more difficult does radiological interpretation become, until when the mastoid process is acellular, we have to report to the otologist that we can give no radiological opinion on possible infection of the mastoid process itself until actual bone destruction has taken place, by which time, unless the surgeon has acted on the clinical evidence alone, a very dangerous state of affairs may have arisen. In the radiology of the mastoid process, regarded as an isolated anatomical entity in itself, we are dependent mainly on the radiolucency or radio-opacity of the cells, and if these cells are few or absent, as frequently occurs, we are inevitably faced with a difficult or uncertain radiological problem, at the best, and often it is impossible, owing to the density of the mastoid, to determine whether infection is present or not. It was the frequent occurrence of this difficulty which induced me to reconsider the whole problem of the radiological investigation of infection in the temporal bone.

Mastoiditis, except in very rare cases, is not a disease entity in itself, but a sequel to infection of the middle ear, resulting from organisms in the nasopharynx gaining access to the eustachian tube and so passing into the middle ear.

The logical approach to the problem would be to X-ray this path of infection, namely the eustachian tube, petrous bone and middle ear and, finally, the mastoid process. This technique, if adopted, will materially help us in the radiological recognition of otitis media in all types of mastoid process, particularly where the mastoids are acellular or poorly pneumatized and where inspection of radiographs of the mastoid process gives us little or no information.

Radiographic Technique

Apparatus.—Though radiographs of the temporal bone can be taken on the ordinary radiographic couch, more satisfactory results are obtained with apparatus specially designed for the purpose, the best known being those designed by Law, Granger, Lysholm and Bullitt. They all immobilize the patient's head in an accurate and standard position so as to show clearly the parts required, with the minimum superimposition of other structures. I use the same upright radiographic stand which I designed for the radiography of the accessory nasal sinuses.

By the use of a rotating anode tube detail is considerably increased and the exposure time reduced to one or two seconds, a great advantage with children. It is essential that only radiographs giving the finest possible detail should be used.

Radiography

(1) *The submandibular vertical position.*—The patient sits with his back to the Potter-Bucky diaphragm, the neck extended back as far as possible, the vertex placed firmly against the diaphragm and the head grasped by the head clamp in the bitemporal diameter. The tube is adjusted so that the central ray is parallel to the posterior margins of the ascending rami of the mandibles and midway between them. The centring of the tube and the position of the patient's head must be very exact, otherwise the shadow of the tympanum will be largely concealed by the petrous bone or the mandibular condyle.

Fig. 1: This view shows the eustachian tubes, the middle ears, the head of the malleus, the petrous, the external meati, and an axial view of the mastoid processes. The eustachian tube shows as a fine negative shadow, due to its air content, running inwards and forwards to the nasopharynx. If occluded, its shadow will be faint or invisible.

(2) 30 *degree fronto-occipital position, or Towne's position.*—The patient sits with his back to the Potter-Bucky, the occiput resting against it, and the head is grasped by the clamp in the bitemporal diameter. The chin is tucked into the chest, so that the orbitomeatal line is 10 degrees above the horizontal. The tube is angled 30 degrees downwards and centred 1½ inches (3·75 cm.) above the nasion.

Fig. 2: This view shows the petrous bones and the internal auditory meati. It also, like the previous view, shows an axial view of the mastoid processes.

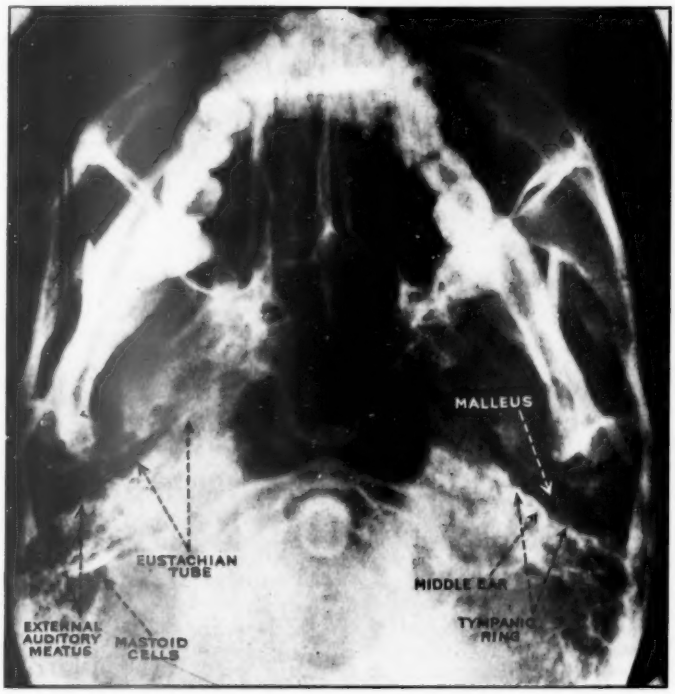


FIG. 1.—Normal submandibular vertical view.



FIG. 2.—30° fronto-occipital view. Right side normal, acute infection left side.



FIG. 3.—Normal lateral oblique.



FIG. 4.—Normal postero-anterior oblique.



FIG. 5.—Note increased density of (A) middle ear, petrous bone and mastoid cells on affected side.

(3) *The lateral oblique views.*—The patient sits with the side of the head resting against the Potter-Bucky diaphragm, in the right or left true lateral position, the head being immobilized by the clamp grasping the occiput and forehead. The tube is angled 30 degrees downwards and centred over the external meatus nearest the film.

Fig. 3: This view shows the extent to which the mastoid cells extend backwards towards, and possibly beyond, the lateral sinus, forwards towards, and possibly into, the tubercle of the zygoma, and upwards into the squamous. It also shows the anterior wall of the lateral sinus, the temporo-mandibular joint, the external meatus and the tegmen tympani and antrum.

(4) *The postero-anterior oblique views.*—The patient sits facing the Potter-Bucky, the orbitomeatal line being at right angles to the film and grasped by the head clamp in the bitemporal diameter. It is then turned through 45 degrees to the right for the right mastoid process and then 45 degrees to the left for the left mastoid process. The tube is centred over the posterior border of the mastoid process.

Fig. 4: This view shows the mastoid process and if, and to what extent, the petrous is pneumatized; it also shows the labyrinth and the internal auditory meatus.

Radiological Interpretation

Acute Otitis Media in a Cellular Mastoid

In the earliest stages of an acute otitis media, only a slight haziness of the periantral cells will be seen gradually spreading throughout the process. At a later stage, the cell walls become decalcified and, therefore, indistinct. This haziness of the affected side at first may be so slight as to escape notice in the postero-anterior and lateral-oblique view where the rays are passing through only a cross section of the process.

Frequently, however, the diagnosis is assisted, as Pancoast and Pendergrass have pointed out, by the anterior wall of the sinus plate on the affected side being thrown into relief in the lateral oblique view. I suggest that this is due to the fact that normally the air-filled cells tend to conceal the sinus plate, acting as a sort of camouflage. When, however, the cells become even slightly cloudy, this camouflage is diminished and the sinus plate then stands out more clearly. Whatever the cause of it, the increased clarity of the sinus plate is a valuable sign in the early stages of acute infection. When, however, in such a case, one examines the radiographs taken in Towne's and the submandibular vertical positions, the slight cloudiness of the cells becomes much more apparent and in the latter position (Fig. 5) not only is the cloudiness of the affected cells clearly seen, but the path of infection is visible also and we note the cloudiness of the eustachian tube and middle ear on the affected side with consequent blurring of the outlines of the ossicles.

In many acute cases, but not in all, one also observes some increased density of the petrous bone on the affected side, as seen in the submandibular vertical view. In chronic cases, of course, it is easy to account for this increased density of the petrous bone by sclerosing osteitis, but it is difficult to understand why this increased density should occur in the early stage of infection in some petrous bones which show no visible cells anterior to the labyrinth. I think the most probable explanation is that in most petrous bones there are peritubal cells present, but that often they are too small to be visible as such through the dense overlying bone. When infected and œdematous, however, their shadows, in proportion to their number, are sufficient to add to the normal density of the petrous bone.

Fig. 5: This is the submandibular vertical view of this case, demonstrating the increased density of the petrous bone and also the cloudiness of the middle ear and mastoid cells.

Acute Otitis Media in the Acellular or Diploetic Mastoid

Up to now, I have been considering the X-ray evidence of acute infection in the cellular type of mastoid. In such cases, the cloudiness of the cells on the affected side, combined with the changes in the middle ear, eustachian tube and petrous bone, make the diagnosis a comparatively simple matter. But if we confine the scope of our X-ray examination to the mastoid process alone, we are faced with a difficult problem in the poorly pneumatized or infantile type, and the fewer the cells the more difficult our problem becomes.

A step further and we come to the completely acellular mastoid (Fig. 6). Here it is impossible to detect any X-ray evidence of infection in the usual views of the mastoid process until actual bone destruction or bone sclerosis has occurred. In such a case, therefore, X-ray examination of the mastoid process alone, for signs of early infection, is useless and all we can do is to inform the surgeon that the process is acellular and indicate to him that because of the lack of cells and, therefore, the anatomical opacity of the process, any radiological indication of the presence or absence of infection is impossible.

If, however, we do not confine ourselves to the examination of the mastoid process (Fig. 7), but study the path of infection in the submandibular vertical view, the problem is solved and the diagnosis obvious. On the right side, the petrous bone is of normal density, the middle ear and eustachian tube are clear and the malleus is well defined, whereas on the left side the petrous bone is opaque, the eustachian tube and middle ear are cloudy and the ossicles are blurred and ill-defined.

Apart from the diagnosis of otitis media, this method of examination is of use in cases of otitis externa, where it is often clinically impossible to determine whether the infection is confined to the external ear or is the result of a discharge through a perforated drum from a primary otitis media. In the first instance, the middle ear will show a normal X-ray appearance, whereas the other will show the evidence of infection.

Chronic Otitis Media

If the infection does not subside, chronic disease of the middle ear supervenes and may persist for months or years. Chronic otitis media practically never occurs except in the poorly pneumatized infantile type of mastoid. The X-ray changes are usually fairly obvious and are those of sclerosing osteitis. If some cells are present, their walls are, at first, indistinct due to decalcification, but as the resistance to the infection is built up, the walls become thickened and dense. The bony walls of the middle ear are thickened and its cavity opaque, so that the ossicles become difficult to distinguish or disappear altogether. This disappearance may indicate actual destruction, or it may be due to a combination of decalcification and concealment by the opacity of the infected middle ear. The petrous bone assumes an ivory-like density and the eustachian tube on the affected side usually shows a lack of aeration.

Complications of Mastoiditis

Abscess formation.—As a result of infection, the walls of one or more cells may break down, with coalescence of the cavities and the formation of an abscess (Fig. 8).

In the differential diagnosis: Cholesteatomata are fairly common and occur in a poorly pneumatized or infantile type of mastoid. Abscess cavities are not common and though they may occur in the infantile, they are more commonly seen in the adult type. Again, cholesteatomata originate in the attic and spread to the aditus and antrum, whereas abscesses are inclined to be peripheral.

Apical petrositis.—Petrositis is an uncommon complication of acute otitis media. It indicates an infection of the cell walls of a pneumatized petrous bone, with actual destruction of the walls. It is associated with Gradenigo's syndrome—paralysis of the VI cranial nerve and trigeminal neuralgia, brought about, some say, by a localized meningitis at the apex of the petrous bone. In the great majority of cases, the diagnosis is a clinical rather than a radiological one, for increased opacity of the petrous bone is a common accompaniment of otitis media and, therefore, this radiological sign alone must not be taken as positive indication of what is clinically known as apical petrositis. The first available radiological evidence of this condition will be an actual breakdown of the bony structure, with possible sequestration.

Cholesteatoma.—Cholesteatoma of the temporal bone is a not uncommon complication of chronic otitis media and requires two conditions for its formation. First a low-grade chronic infection and a mastoid process of the infantile type. In such a mastoid, if the infection is of some virulence, the cells and diploetic bone are invaded by the organisms and a diffuse bone infection takes place. But if the organism is of low virulence, a much slower process occurs in the highly resistant bone. The normal mucosa of the middle ear is gradually destroyed and replaced by epidermal cells, either by extension of the epidermis of the external meatus, through the perforated drum, or by cellular metaplasia. These cells undergo a constant process of destruction and replacement, and the dead cells accumulate in a pseudo-tumour which gradually increases in size as further dead cells are added to the mass.

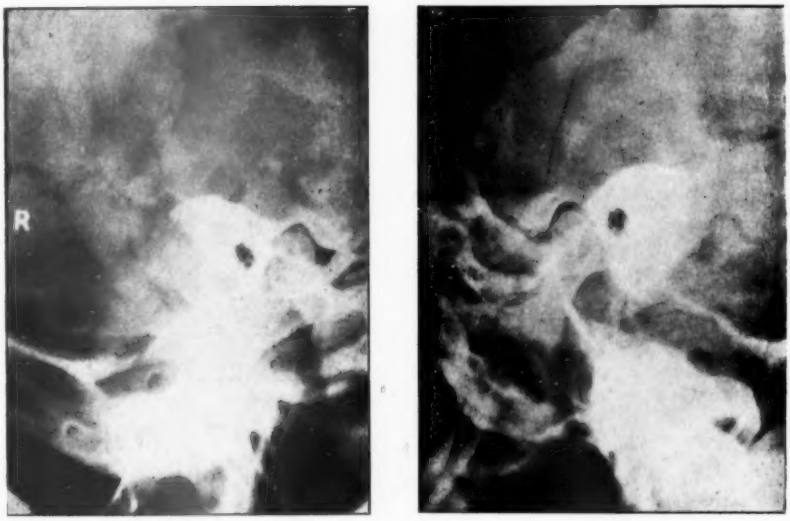


FIG. 6.—Acute left otitis media in acellular mastoid showing no X-ray evidence in usual views of mastoid process.

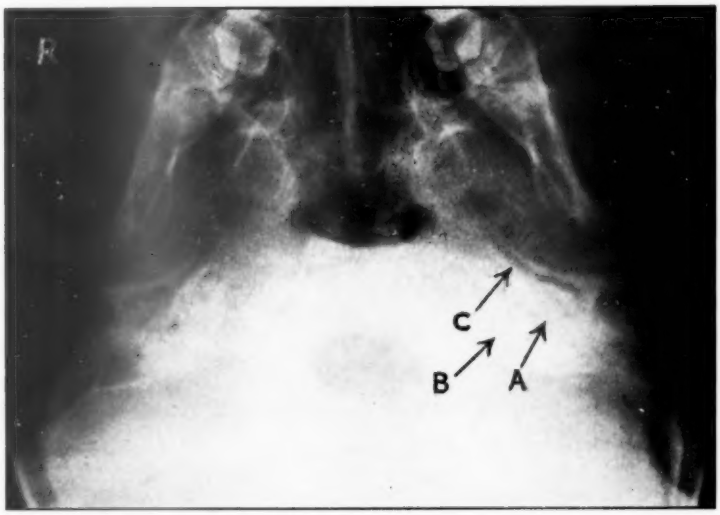


FIG. 7.—Same case as Fig. 6. Submandibular vertical view showing opaque left middle ear (A) and increased opacity of left petrous bone (B) and eustachian tube (C).



FIG. 8.—Perisinus abscess.

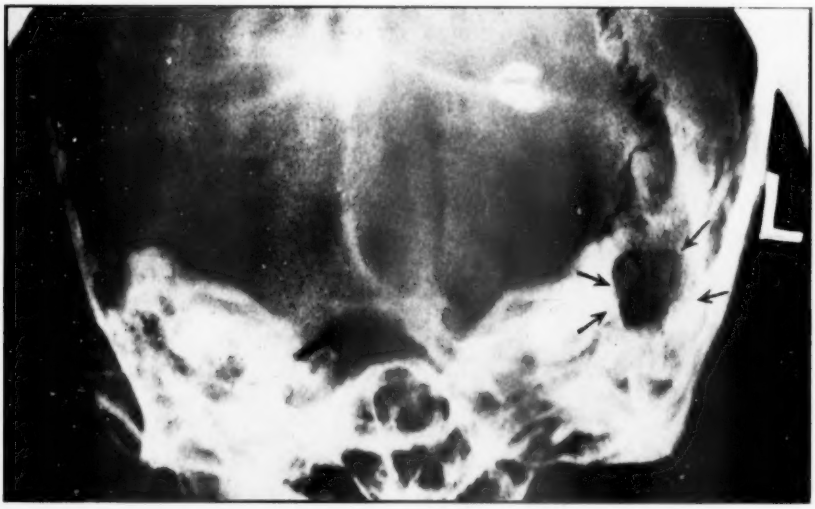


FIG. 9.—Cholesteatoma.

Acknowledgment.—The ten figures illustrating this paper are reproduced by permission from "Textbook of X-ray Diagnosis", Vol. I, 2nd Ed. 1951. H. K. Lewis, London.

This mass originates in the attic, from whence it may extend through the aditus into the mastoid antrum. When the mass completely fills the cavity it occupies, the bony walls, softened by infection, commence to be gradually eroded by the pressure of the tumour (Fig. 9). Until this erosion is of an appreciable extent, and the cavity is obviously larger than its fellow of the opposite side, the only evidence in the radiograph will be that of chronic otitis media. Negative X-ray evidence of cholesteatoma, therefore, does not by any means signify its exclusion. Owing to its slow growth (Fig. 10) a protective zone of calcification occasionally forms in the bone around the periphery of the mass. The eroded area, which is less opaque than the surrounding bone, is usually smooth and oval or round in shape, but it may be irregular where some cells are present, the walls of which are broken down. The importance of early diagnosis of the condition is that as the erosion increases it may perforate through the apex of the external canal of the labyrinth, causing a labyrinthine fistula through the upper part of the posterior wall of the external auditory meatus or through the tegmen tympani into the middle fossa.



FIG. 10.—Cholesteatoma. Note thin line of calcification around upper part of cavity.

Healed otitis media.—If the infection has been of sufficient severity and duration, the radiographs will show abnormal density of the middle ear on the affected side. The ossicles may or may not be visible and the bony walls of the middle ear, the petrous bone and the mastoid process will show a varying degree of sclerosing osteitis. If the process is cellular, some or all of the cells may be completely obliterated by sclerosis of the walls, and the visible cells may be cloudy, due to granulations and chronic hyperplasia of the mucosa.

Where a superimposed acute infection occurs in such a mastoid, it is often impossible to detect it radiologically. Occasionally, if one is fortunate enough to possess radiographs taken before the re-exacerbation, or the circumstances of the case permit serial radiographs to be taken at a few days interval, X-ray changes may be discernible. In such cases, fresh areas of bone absorption or sequestra may be seen, but, generally speaking, realizing the very great difficulty of the radiologist in giving any useful information, the otologist will act entirely on his clinical judgment. Unopened cells are often difficult to detect. The otologist, at operation, may have broken down the cell walls, leaving the thicker bases of the cortical plates of the cells. These circular shadows may mislead us by simulating complete cells.

SUMMARY

(1) The anatomical information given by the radiograph is of primary importance, as the course of infection in the petro-mastoid is largely determined by its anatomical type.

(2) Mastoiditis being a sequela to otitis media, the primary X-ray evidence of infection should be sought in the path of infection, namely the middle ear, eustachian tube and petrous bone in all cases.

(3) Where the mastoid is acellular, and we are therefore unable to give any radiological assistance by study of the mastoid process itself, examination of the path of infection will usually give the information we require.

Dr. J. Blair Hartley entirely concurred with Sir Harold Graham-Hodgson's opinion that the submento-vertical view through the temporal bones was of the greatest value, and should always be taken when an X-ray examination of these bones was being made.

He then showed a lantern slide of this projection, which he claimed to be probably one taken at the earliest age yet seen by radiography. It showed the base of the skull of a stillborn infant of 36 weeks' development, from which the skull had been dissected out, so that the base might be studied.

Dr. Hartley thought that Towne's view was almost equally essential to complete examination of the temporal bones, and added that stereoscopic Towne's views were even better.

Examination of the accessory nasal sinuses really constituted an essential part of the investigation of the temporal bones, and the reverse was equally true.

Dr. R. A. Kemp Harper asked Sir Harold Graham-Hodgson's opinion of the value of Meyer's view, which he had found very useful in the demonstration of certain types of cholesteatoma not definitely demonstrated by other views in common use.

Lantern slides were then shown of a patient who had had a radical mastoid operation many years before and who had recently complained of some discharge from the same ear. X-ray examination of the patient revealed an enormous cholesteatoma destroying most of the petrous temporal bone and almost the whole of the internal ear. Several sequestra were also seen. Operation on this patient had revealed that there was a huge cholesteatomatous mass lying immediately under the dura of the middle and posterior fossa, and the whole vestibular apparatus was lying loose in the cavity except for its attachment to the acoustic nerve.

Sir Harold Graham-Hodgson (*in reply*): I agree with Dr. Blair Hartley that stereoscopic views are often useful and that examination of the accessory nasal sinuses also would often be an advantage; but this procedure would involve the possible risk of overexposure, since repeat radiographs in a few days are often necessary.

I agree with Dr. Kemp Harper that Meyer's view is sometimes useful in cases of cholesteatoma, but generally speaking I prefer the other views.

Section of Psychiatry

President—W. J. T. KIMBER, D.P.M.

[*June* 13, 1950]

DISCUSSION ON THE TREATMENT OF OBSESSIONAL NEUROSES

Dr. Emanuel Miller: It would seem desirable in a symposium of this nature in which there is likely to be a sharp dichotomy in both practice and theory, for the disputants to make clear their standpoint and experience.

For my own part although I do not carry a trade union card I wish it to be understood that I occupy no eclectic position in which the best is so often the enemy of the good. I accept the classical Freudian psychopathology with a few reservations: of these reservations I would cite:

(1) Due regard to the presence of psychotic undertones which have been elucidated by Klein.

(2) Due regard to the inborn constitutional factors which, once classified, must influence any optimism with which the interesting unconscious dynamics might suborn our prognostic judgments.

Despite my conviction of the value of Freudian psychodynamics in giving meaningful structure to both character and its various neurotic and psychotic disorders I feel myself free to vary my practical approach by the use of ancillary methods such as narco-analysis, abreaction techniques and analytical interpretations where full analysis is economically impossible or undesirable for dynamic reasons. I hold strongly to the need for careful ancillary personality studies before analysis is decided upon. These are particularly valuable in hospital and clinic practice where leisurely procedures of analysis at long term, yielding deeper insight, may prove uneconomical.

And indeed while I have a quite irrational abhorrence of brain slicing, I think that we are justified in certain circumstances of threatened disasters to recommend the Frankenstein approach.

What renders the problem of obsession-compulsive states difficult is not solely the bewildering variety of its manifestation but the relation they bear in psychopathology to certain conditions which can be more simple in structure or infinitely more complex. By the former, I wish to imply less difficult of resolution, in that they derive from later stages of mental organizations; by the latter I refer to those disorders which are mainly psychotic in character. I regard the distinction as important, for choice of treatment will rest on this distinction.

In their relation to the less complex state, reference is here made to anxiety proper and to phobic states.

In looking through case records from 1925 onwards of persons seen by me, I note the frequency with which presenting anxiety symptoms were associated with (*a*) obsessional personality traits and sometimes actual obsessional and compulsive symptoms and (*b*) phobic symptoms held with obsessional force and transformed into obsessional rituals of great elaboration developed for the purpose of the avoidance of the phobic situation. The possibility and advisability of analytic treatment will rest upon recognition of these variants.

With respect to the first and second, I can select examples which are representative of these groups.

(1) A man aged 45. Growing sense of dislike of his wife who had traits representing the obverse of an obsessional person's ideals, she was slatternly, had a body odour and while she had sex appeal he found he was obliged to reduce desire for intercourse, unless she expressed the wish. He is meticulous, highly moral, and "I would rather die than be unfaithful". Last February he developed acute cardiac pain and dyspnœa, with little exertion. This proved to be associated with sudden realization of the attractiveness of his secretary. This he met with all his feelings of righteousness and sexual restraint. Having received assurance of a normal heart and lungs, he found himself with an increasing hostility to his wife's untidiness and an increase in his sense of orderliness and cleanliness. He has also a residual phobia of cardiac failure despite a cardiologist's repeated reassurances. He now cries out for a ritualized life which will check his dread of his symptoms.

Treatment has already led to a pronounced improvement. This "cardiopath" is now more aware of his moral problem and its source.

(2) A young man of 29, a musician, single, had a sudden fainting attack while attending a play. For some weeks he remained anxious and fearful of playing in the orchestra lest he should faint again. Just before the onset his mother had dissuaded him from marrying a girl whose family was not socially acceptable to her. A week after he came to see me, he read of the murder of Raven's father- and mother-in-law. He suddenly became obsessed with the thought of murdering his mother. The anxiety attack occurred in December 1949. His parents were maladjusted to one another and lived apart. His two sisters have parted from their husbands.

Prior to the breakdown his personality was intact, but he fainted when called up for service but served well for two years, when he was discharged for anxiety neurosis.

There were no signs of obsessional or compulsive behaviour, and apart from features of mother fixation no signs of neurosis or behaviour disorder occurred in childhood and puberty. Always characterized by procrastination.

Nevertheless, with the continuation of treatment the compulsion has abated or, more accurately, has been replaced by a mild depression expressed in loss of interest in his work and feelings of great exhaustion. Analysis has been cramped by his working hours and has been conducted by analytic interpretation of dreams, and day to day situations which seemed inexplicable to him.

Such improvement as can be registered is due to an intact personality and the relatively partial invasion of the compulsive process.

(3) A woman of 45, married, one child. Marriage successful. Highly endowed, artistic. Last January suddenly felt sick and weak in the legs while on holiday and about to see her daughter off to bed. Since then she has had a phobia of being alone or out alone lest she has another attack. She has had great flatulence all her life, made worse after appendicectomy thirteen years ago.

Last March, while still controlling her phobia by having a companion or her husband to take her around she suddenly thought she would murder her child. Compulsion to suicide while near a window alternated with this thought. Both compulsions have been minimized by 1 grain sodium amytal per day. She is in the early stages of treatment and the flatulence as well as the attitude to the child are becoming closely woven together as a result of the dynamic relations being made clear.

(4) A less favourable example is that of a man of 55, successful industrialist; one son. He comes from a family of five, all exceptionally gifted in the fields of art and science but distinctly unstable and rebellious in their family relations, and loyalties, but no neurosis. He is the least rebellious, devoted to parents who were separated. Exhausted himself with social welfare work and helping underdogs.

Developed a cardiac neurosis seventeen years ago and did much "welfare work" in supporting cardiologists in Harley Street. Last year he lent his son his razor and felt compelled to murder him. He has had repeated compulsion thoughts of slashing his own throat and wrists.

Treatment has been impossible by the psychological route because there is repeated oscillation between periods of cardiophobia and periods of compulsive anxiety of profound degree. He feels he is kept going by paying tribute to Harley Street. He refuses leucotomy on grounds not of fear of operation, but because of loss of prestige he feels it would entail.

In surveying my case records I find that the compulsive states as compared with obsessive ruminative states are much more prone to remissions or to the supervention of somatic anxieties.

For my own part I should be prepared to say that the ruminative type of obsessional and those held within the grip of imperative rituals are extremely difficult to treat by analysis and I think for several reasons.

The logic of such patients is not only tightly woven but held with skill born of the high intelligence with which they are so frequently endowed.

Attempts at free association are met with repeated secondary logical elaborations which act as something more than ego defences. The logic is used at most elementary levels and if broken down by the analyst's attempt at too early an interpretation however valid, more primitive reaction formations assert themselves in the form of paranoid and depressive reactions preceded by phases of very acute anxiety. This I believe to be due to the patient's difficulty in handling ano-sadistic phantasies disguised by the myth and magic of the ritual or the thought defences.

To this degree efforts at abreaction are dangerous. In one case a compulsive ruminator was disclosing œdipal phantasies which seemed to screen deeper pregenital guilt, and an acute psychotic depression supervened. In this, anxiety was uppermost and was dealt with as such by the transference being deliberately maintained at a conscious uninterpreted level, while the psychiatrist in control was able to maintain a good father role standing opposed to the mother whom the patient feared and a bad devouring beast, an introjection of his early oral sadism. During the period of conscious support he was able to return to work with minimal compulsive symptoms. I have no time to cite other examples in which the abreactive approach had made the patient materially worse. In my view no case of obsessional tension should be treated by reinforced abreaction. In most cases of compulsive neurosis the compelling act with the exception of the obsessional compulsive ritual is very close to the primary impulse, and if this is suddenly released a psychosis can be precipitated.

A word or two must be devoted to the obsessional compulsive states in young subjects with intimations of schizoid personality traits. Before embarking on deep psychological treatment it is worth devoting considerable time to a careful personality study to ascertain whether beneath such adolescent obsessional thinking there is not screened a larval schizophrenia. To quote an example, a boy of 15 of I.Q.135, had extreme obsessional rumination well held together by excessive circular thinking. Against my wishes the parents sent him to someone for analysis. Within six months he became schizophrenic. Alarmed by the change the psychiatrist sent him for a course of deep insulin coma. He made a recovery within nine months and was preparing for his matriculation. He then returned to his obsessional

rumination state with many superadded rituals. There are some, no doubt, who could and would administer full length psychoanalysis. He was not in my view the impulsive type, who would have been chosen for leucotomy. Nevertheless, the Rosen technique might have done something for this lad.

A further example can be quoted here:

Patient depressed for six months, aged 21. Had held no job after fifteen tries. E.C.T. nil result. Behaviour became violent. Insulin coma in 1941. No result. Violent. Leucotomy followed at Barnwell. Personality change. Has become progressively obsessive. Washes 15 times a day. Changes four times a day. Obsessed with need for plastic operation. Ritual behaviour in walking. Molests people in endless talk. Would a second leucotomy be recommended?

Constitutional factors apart, psychoanalysis has clearly shown that the roots of compulsive-obsessional behaviour lie in childhood, in the battle between two forces: the early object relations associated with oral and anal interests and the cultural methods of nurture varying in different social groups.

Obsessional and compulsive behaviour is all too common in childhood but then prognosis is by no means unfavourable particularly if personality deviations are discovered early and receive treatment; that is treatment of the child, and treatment also of the parents with respect to their nurtural techniques and their own carry-over of obsessional traits and demands. In children it is noticeable how little troubled they are by their own obsessional behaviour—some seem almost to accept them as a part of life—like play itself; indeed the obsessions are in the nature of an acting out. Some children of high intelligence exhibit some of the sophistication of adult ruminators. Interpretation during play can be met by subtle arguments used as defences against insight.

Nevertheless, despite this difficulty the transference once established makes it possible for the child to play out aggression phantasies which can be explained in the play situation. To the parents this interlude of aggressivity in what has been a controlled and obsessive child can be disconcerting and they may wish treatment to cease.

The compulsive child is frequently also phobic and while in these cases the child's distress is real and sometimes intense, play therapy is very helpful and hopeful. I do not feel that leucotomy should be even thought of, let alone practised in any child before puberty.

Prognosis is not always good for treatment in cases when there is abnormal E.E.G. But even where immaturity is a pronounced feature with poor ego development, a benign regime analytically informed is the best order of life to adopt with no direct treatment at all by a psychiatrist.

In closing, I beg to sum up, thus:

(1) The type of obsessional compulsive of extreme degree is rare, and may seem to be less so when they gravitate to certain psychiatrists who are known to specialize in this type of disorder. This extreme type is usually so narcissistic with minimal powers of transference that analysis is impossible unless the analyst starts with no high hopes and the patient is prepared for years of treatment. We must admit that these unfortunates ultimately reach a neurosurgeon.

(2) The milder case particularly with phobic interludes or with phobias held in check by obsessional-like means can and should where possible be given the opportunity for systematic analysis on long term. Here too a qualification must be made. Where constitutional factors can be demonstrated and where signs of personality immaturity are clear in the early stages of investigations a more supportive type of treatment is indicated by, if possible, a psychiatrist with good psychopathological insight.

(3) Where the personality in general is involved and there has been an uninterrupted history of maladaptation, the ego is clearly poorly developed and analysis is not likely to be fruitful.

(4) I do not think that the goal-pursuing method of Finesinger yields good results.

(5) As Schilder has suggested careful examination of the logical constructs of the ruminator may present the subject with weak points in his defences, and when he realizes the defensive nature of his constructs the superstructure falls, but we must be prepared for underlying psychotic dynamics being revealed. These types keep all the defences in the front line, and leave their lines of communication weak with the danger of resurgence of depression.

(6) Young persons, particularly children, should not be despaired of. While personality is still plastic prognosis is good.

(7) No one should object to leucotomy in extreme types. Neurosurgical theories apart, it is the best practical, if last, resort.

There exists an infinite gradation not only in the quanti ative aspects of obsessional neurosis but in the grading from phobic disorders on the one hand and depressive states on the other. No black and white choice of therapy or prognosis can be made. The issue is not simply Freud or Frankenstein.

Dr. Karin Stephen: It is not so easy to say why any given person, if he *does* become neurotic, becomes obsessional rather than, say, hysterical or paranoid.

Psychoanalysis believes that neurosis is the after-effect of damage to the personality when it was immature and very vulnerable. A child's personality may be damaged if it suffers too much or becomes too frightened when it has to endure severe or prolonged deprivation or over-stimulation. When children are badly upset they react, instinctively, with some sort of reflex defence to try to ward off the pain and danger. In an extreme emergency the personality may simply take flight by turning a blind eye, just blotting out the whole thing; much in the same way as the body deals with intense physical pain by fainting, or the eye protects itself from a dazzling light by blinking. Of course it is not only children who are going to grow up neurotic who get hurt and frightened; such things are bound to happen to everyone. It would not only be impossible but even detrimental to try to shelter a child completely from the frustration which the vast disproportion between its demands and what reality offers inevitably imposes. A human being can only live successfully by learning to deal with such experiences, so that the best that can be done for a child is to temper the wind, especially at first, to let it enjoy full satisfaction at least sometimes, so that it may not lose heart, and to come to the rescue when it is too hard pressed so that it is not called upon to bear more than it has strength to endure and so to get over. (There are limits, too, to what parents can or should endure.)

Where neurotics differ from more normal people, is that for some reason, *what they had to endure was too much for them*, so that *they never succeeded in getting over it*. It is true that they no longer consciously remember what happened originally but, at some deep level of their minds, they are still brooding over it and their personalities are still organized defensively against ever having to go through the same sort of thing again, or even being reminded of it. Rather than risk this they recoil, instinctively, from everything which tends to revive the memory of what happened or seems to threaten its happening again, much as a person with an unhealed wound might wince away from being touched on the sore spot.

Unfortunately this reflex withdrawal from contact can have disastrous consequences. The purpose it served, originally, was *to insulate the child* in a crisis created by an intolerable mixture of pain and fright, provoking reactive rage and counter-attack or despair and collapse, which it could not bear to face. It may have been the only thing to do, then, but if this sort of reflex defence is kept up long after the original state of emergency is over, and becomes built into the character, it *shuts an important part of the self off from the rest* and *breaks its contact with the outside world*. If this part of the self remains *too successfully insulated* its development is arrested, it remains "fixated" to the old childish situation, unable to take in the new experiences which would modify or correct its earlier impressions and attitudes, so that it never outgrows and gets over the past—the old wound never gets a chance to heal. In some unconscious, subterranean region of the mind it carries on a separate existence, still wanting what it was originally deprived of, still frightened and angry, or despairing, afraid of its own violent and conflicting urges, out of touch with real life, still blindly defending itself against anything which seems to threaten to revive the old intolerable experiences of childhood.

The more rational, conscious part of the self lives its everyday life oblivious of this submerged childish part, except when this other self gets the upper hand. Then the personality loses touch with reality and commonsense and finds itself thinking and behaving in the cautious, irrational ways which we call neurotic, which would only be appropriate if what was happening now was identical with what happened long ago (*or what the child believed was happening*, which is often very fantastic). As far as this fixated part of the self is concerned, it sees no difference between now and then. It is much as if the warding-off reflex by blinking were to stop the eye from being able to see ever after, and the person went on behaving as if he was still being dazzled.

According to psychoanalysis *something of this sort has happened to all neurotics*: their reflex defences have gone into spasm, or, to put it another way, have set up a short circuit, cutting out the long circuit through normal awareness of what is actually happening, so that they go on behaving as if they were still living in the remote past. This is how psychoanalysis explains the characteristically inappropriate neurotic behaviour which we call "compulsive" as compared with the more intelligent, realistic behaviour which we might, in contrast, call "voluntary". Important crises, even those which happen before the psychophysical organism emerges from the twilight state which precedes clear consciousness, leave their mark on it for good or ill, and the evidence shows that neurotic, compulsive behaviour may date back to experiences of pain and danger at any time in infancy and childhood, to troubles over suckling, even to the crisis of birth itself.

Of course if things go better later on a healthy child may get over a very bad start, or, failing that, may find some working adjustment which will enable it to grow up in the way

we are accustomed to regard as normal. After all, there is no hard and fast dividing line between health and illness; the distinction is a relative one. But if bad experiences pile up one after the other the personality may become progressively damaged, and then it will begin to show the characteristic signs of illness. In childhood these are apt to be discounted as mere "naughtiness", or "bad habits", or ordinary bodily ailments; it is only later on that they crystallize into a recognizable neurosis.

As regards the choice of neurosis, no doubt constitutional predisposition plays a greater or lesser part, but leaving this aside, psychoanalysis would say that the form a neurosis takes has a good deal to do with *the stage in its childish development* at which the psychophysical organism had to endure more than it could bear, and with the type of reflex defences it resorted to. For instance, it connects obsessional neurosis with what it calls the "anal " stage, the predominant defence being one of vigorous opposition, reinforced by "over-compensation", as contrasted with the simpler blotting out which is more characteristic of hysterics. We all know how obstinate and covertly rebellious obsessionals are, also how they tend to over-drive and force themselves to do their duty, and how, in particular, they are apt to display a horror of dirt and untidiness, so that they will often wear themselves out in trying to eliminate it. According to psychoanalysis this over-conscientiousness, which wages a heroic though sometimes a losing battle against something in the self which seems determined to mess everything up, shows that the obsessional is still tied to what happened to him at the "anal" stage of his early history, the period in the child's life when it comes up against the problem of learning sphincter-regulation.

At this time it finds itself pushed and pulled in contrary directions, by the outside authorities who insist first that it *musn't* and then that it *must* defæcate, and also from outside itself, wanting to and trying to stop itself. It is a problem in which morals, at a nursery level, and self-preservation too, are involved. The child is confronted with the task of co-ordinating its bodily functions and its conflicting impulses, of steering the right or safe course between abject surrender to authority and bodily urges, and pig-headed resistance or defiance. The way children deal with these two kinds of coercion matters because it sets the model for their later dealings with coercion in all forms.

On the purely physiological level it is not a simple matter to acquire this sort of realistic self-regulation, but, for a child of this age, wider issues are involved concerning the regulation, not merely of its bowel functions, but of its passions, which is an essential part of character-formation. In early life defæcation means much more than the mere elimination of the waste products of digestion: for the child it is at times an urgent need whose satisfaction gives an intensely pleasurable sensation; also it is a creative act, and an act through which it expresses powerful emotions.

Human beings of all ages use their bodies to express their loves and hates. In babyhood, when they are angry, they scream and kick: sometimes they bite. It is an old wives' tale that babies distinguish those they love by wetting on them, and if psychoanalysis is right, both love and hate can express themselves through defæcation too. When the child is in a good mood its fæces mean to it love gifts, so that, when the beloved adult treats them as worthless and scolds the child for producing them, it feels humiliated and rejected and very depressed or resentful. Deep down the child may cling to its own over-valuation of the precious substance, but at the same time it may turn against it in anger or despair, and it may even turn against or despair of itself too. I remember a patient whose whole manner and train of thought suggested that he was in touch with a bygone experience of this sort, holding out his cupped hand and exclaiming bitterly "they dash it out of your hand". Then he actually remembered that, at the age of 3 or 4 he had offered his mother a piece of his fæces and she had struck away his hand in disgust.

When the child is in a bad mood its fæces mean dangerous expressions of hate, bombs with which it intends and believes that it is able to blow the adults up, and perhaps itself too, so that the adult's insistence on its defæcating at such times may well feel to the child like an incitement to murder, or suicide.

For the obsessional who is fixated at the anal stage, defæcation and fæces still have these powerful love-hate meanings, and, since he has never got over the childish humiliations and rebellious rages provoked by his nursery experiences, intense, often murderous hate is predominant. He is inclined to hoard his precious product, refusing to cast his pearls before swine, or to regard it as a dangerous explosive which he may long to fire off but also fears to let loose, all of which explains why obsessionals are inclined to be constipated.

But this childishly fixated reaction pattern is not confined to his own bodily products. The obsessional wrestles to get the better of every kind of dirt and untidiness as if they were fæcal "messes", and disapproves or is terrified of them, but also secretly delights in them, and this identification with anal matters spreads over a still wider field, applying to doing one's duty in any sphere, to all sorts of work and creative activity, and also to all the tensions and conflicts set up by the vital urges, including sexuality.

To all needs and longings and to all outside coercion, even to the restrictions imposed by the laws of nature, especially by time, the obsessional reacts according to the old, blind, reflex pattern of "mustn't do it, must do it", "will do it, won't do it", "will do the exact opposite", with which he reacted originally to his own bowel urges and to the pressure put on him to be a good, clean boy, and he is inclined to treat all possessions, notably money, as if they were his own prized, rejected, dangerous fæces, to be hung on to obstinately when others try to make him part with them, or doled out cautiously, or despised as "filthy lucre".

I don't know how accustomed psychiatrists are to regard behaviour in terms of this tendency to equate situations which have some resemblance, though in important respects they may be very dissimilar, to react to them all according to an identical pattern.

One of the striking facts psychoanalysis has drawn attention to is how prone human beings are to "displace" the significance of old events on to new ones, and how, in neurosis, this is carried to extreme lengths. Imagination, of course, does this, and we do it too whenever we argue by analogy, but if drawing analogies is not to mislead us we need to pay attention to differences as well as to likenesses, otherwise we cannot learn by experience.

I suppose it is because they lack this power of taking in the unexpected that the behaviour of such creatures of instinct as ants is so stereotyped. The neurotic's state of mind, at an unconscious level, seems to be much like the ant's. His behaviour too is stereotyped, he has failed to learn by experience.

The obsessional's tendency to react to all kinds of compulsion as if they were interferences with his freedom to open his bowels is a case in point. It would be interesting to hear what the anthropologists could tell us about what happens to people in other cultures which do not make such a point of cleanliness training as we do. Do they get "anal" fixations too? It *would* be interesting to know, but it would be wrong to suppose that anal fixations are all due to mistakes in upbringing, and that everything would be all right if children never learnt control at all. After all it is natural enough that children should get alarmed when forces inside themselves threaten to run away with them, especially if they are forces of destruction, and defæcation is a very powerful force, and when it is used to express uncontrollable rage its meaning *is* very destructive. So, quite apart from outside interference, children might well react to this internal danger defensively, and no doubt they all do at times.

Neurosis only results when, instead of being outgrown, this reflex defensive attitude gets built into the character. The great problem in explaining the cause of neurosis is to discover why this happens in some cases and not in others. Put briefly, it seems to have something to do with *the excessiveness of the original pain and danger and the contradictoriness of the reactions simultaneously aroused, relative to the personality's powers of endurance and co-ordination at that time*, and also, perhaps, to do with *the degree of shock*.

On the question of the suitability of obsessionals for psychoanalytic treatment, I should say that, so far as we know, there is nothing in the obsessional type of defence as such, nor in the fact that the fixation appears to be at the anal level, to contra-indicate analysis, and indeed some obsessionals do very well, though progress is apt to be slow because their defences are tough. But *if the personality is very rigid this may be taken as a danger signal*, warning us that it may be unsafe to tamper with its defences.

Response to treatment, cure, would involve relinquishing the reflex type of defence on which the personality is relying, to replace it by some more flexible and more reality-adapted kind of self-regulation. Great rigidity of personality structure may mean that its capacity to make this readjustment is weak or non-existent. Its *only alternatives may actually be, either to keep the neurosis or to go to pieces*, in which case it would be better to leave it alone.

This, perhaps, really comes to much the same thing as saying that *a severe obsessional neurosis may mask a psychosis*, a point on which there is general agreement. Underneath the rigidity which does at least enable the patient to keep going, *there may be schizophrenic chaos*. But even this is not specific to the obsessional, we know that other kinds of neuroses, too, may mask a psychosis.

In regard to the handling of these patients psychoanalysis, with its gradualism and avoidance of force, may be relatively safe as compared with other forms of psychotherapy, such as abreaction under drugs, which make a more frontal attack on the defences. I believe that at present, psychoanalysis is the only psychological approach which offers any real hope of cure.

The psychoanalytic method is unique in that it does not try *to coerce the patient into getting well*, but offers him an opportunity—if he can take it—*of completing the process of growing up*, which was arrested by his illness. To this end *it seeks to gain the co-operation* of the patient's personality (not merely his intellectual consent) in the very difficult combined operation at which the treatment aims. On the one hand it aims at enabling the patient to develop awareness of internal and external reality, of what, at a dynamic though unconscious level, a part of himself really believes and feels and wants and fears, and of what the world is really like and what he may expect from it.

On the other hand it aims at enabling him to develop his own powers of mastery, both of himself and of his outside circumstances, so that, in the light of this awareness, he may be able to choose when to hold back and when to let go.

This change-over from helplessness to mastery corresponds with the change-over from infancy and early childhood to adult life, and with the change-over from neurotic, compulsive functioning to healthy functioning. Again, of course, there is no hard and fast line of demarcation.

To be offered this opportunity, the opportunity in fact to grow up, may indeed be the patient's only chance of recovery, and, this being so, the analyst may decide to attempt treatment even in very severe cases, being fully aware that the undertaking is a formidable one and not free from risks and that, at best, the analysis is bound to be lengthy and arduous, but judging that a treatment lasting even ten or fifteen years may be justified if its outcome in the end is successful, and if the only alternative is lifelong misery. If he decides to make the attempt the analyst will proceed cautiously, bearing in mind the possibility that, as the case develops, cure may prove impossible, either because the patient may defeat the analyst by clinging to his defences through thick and thin, making no progress, or because it becomes clear that his neurosis is the best adjustment of which the patient is capable, so that any change would be for the worse.

If the analyst begins to foresee that to proceed with the analysis will either be useless or positively harmful, he has not burnt his boats, as the surgeon inevitably must. It is still open to him quietly to change over to a less radical, more supportive kind of psychotherapy for a while, after which he can let the patient go in a state at least no worse, perhaps somewhat better than he was when the treatment began.

No responsible analyst would claim that analysis is a panacea which is bound to succeed, nor that it is always free from risk. We know well that *psychoanalysis is a powerful catalyst*. The treatment cannot make any headway without activating the old painful memories and fears and fantasies which, though they may be out of date now, were all too real in early life and, at an unconscious level, are still real to the patient, but which his defences have somehow managed to keep at bay. So analysis must, inevitably, put a strain on the patient's endurance.

No one develops a neurosis without good reason: every neurosis is an attempt to deal with experience which was, originally, and still feels as if it would be, intolerable. However costly it may be in happiness and efficiency, the patient clings to his illness as being the lesser of two evils, since it does at least provide him with a *modus vivendi*. And indeed for some *it may really be the lesser evil*.

Is the patient capable of doing without his neurosis? An experienced psychiatrist can, no doubt, form some opinion, but I do not know of any reliable criteria by which the matter could be judged. Perhaps it would at least be a beginning if we could formulate the sort of considerations which appear to be relevant. At present we have no alternative except to carry on our investigations in the two separate sciences of organic and psychological medicine, each using its own language in its attempts, for instance, to explain the psychophysical happenings which we call neurosis by framing hypotheses in terms on the one hand of physical, and on the other of psychological causal sequences. There is nothing in either kind of hypothesis which contradicts the other: it is not a question of either/or, both may be true and, if each side can make its findings intelligible to the other it may turn out that we can use each other's explanations, in the way that science uses analogies, to throw light from one field of investigation on to the other, and this, perhaps, will help us with our common problem, which is concerned with the functioning of the psychophysical living organism.

My contribution must be to say what I can about how a psychoanalyst would try to determine whether, with the help of analysis, a given patient's personality would be capable of further growth, away from fixation, helplessness and stereotyped patterns of reaction, in the direction of awareness, mastery and self-direction.

Already some analysts, though so far only working in isolation, have begun to experiment with using E.C.T. in depressive cases where, for some reason, the barriers which hinder the patients' mental growth seem to be insuperable by ordinary analytic treatment, and already, in a few cases, they have found that, after shock, the patient has been made able to make better progress than he could before.

This clinical fact is of practical importance, obviously, but it is also highly intriguing theoretically. It is a challenge to us to find out what this electric shock to the brain has done to the patient's personality, not to interfere with its functioning or diminish it capacities, which can easily be brought about by brain injury, *but to make it function more normally*. If the psychoanalysts and those psychiatrists who employ physical therapy would work together on this problem we might learn more about the physical and psychological changes associated with the process of recovery.

Psychoanalysts are not prepared to say definitely that treatment by analysis is suitable for a particular type of neurosis, or that it would be advisable in, for instance, a hysteric, an obsessional, or a paranoic. But already psychoanalysts can say, although as yet only in very general terms, a good deal about the internal dynamics of personalities who are more or less likely to be capable of recovery.

One can try to assess a personality from the point of view of the balance between internal forces or between opposed tendencies, for instance between love, rage and fear, or between seeking for contact and withdrawal into fantasy, between the forces of integration and disintegration (which Freud must have had in mind when he talked about Eros and the Death Instinct). These integration-disintegration tendencies seem to be connected, though not identical, with the opposed tendencies of growth towards maturity and of regression, and with the tendencies to go on hoping and trying or to despair and give up.

One might say, tentatively, that if a personality is too much dominated by rage it may prove too hostile or too much bent on revenge to co-operate with the treatment, or, if it is too much dominated by fear, if may prove too mistrustful. If it is too much withdrawn it may prove inaccessible. If its powers of integration and its growth tendencies, or its capacity to go on hoping and trying are too feeble, it may prove incapable of development.

I believe the consideration of these various balances is relevant to our problem, but as yet we have no precise criteria by which to estimate the relative strength of these opposed forces.

Perhaps the way in which it comes most naturally to an analyst to try to assess the recoverability of a patient's personality would be in terms of the strength or weakness of his Ego.

It must be confessed that the word Ego is not always used with a single consistent meaning in analytic literature and discussion. Sometimes it seems to be used to mean much the same as we should ordinarily mean by the Self. Sometimes, as where Freud contrasts Ego- with Libidinal-instincts, he seems to be using it to mean the forces of self-preservation. Elsewhere, when he is describing the psychophysical organism "topographically" rather than dynamically Freud speaks of the Ego as the part on the surface which makes contact with what is outside it, whose function is to mediate between the organism's needs and desires and the outside world in which they seek satisfaction.

The Ego's task is *to be aware* and make *intelligent judgments* in the light of experience, so that it may direct the forces of the Id relevantly and appropriately.

In this meaning, which is the one that concerns us, the Ego's function, over and above mere awareness, is concerned with organizing and integrating and co-ordinating, in such a way that the psychophysical organism may be able to act as a whole, purposefully and self-consistently, instead of being pushed about helplessly and disrupted by incompatible and conflicting drives. It would seem to be the Ego, in this meaning, which, in its immaturity, defends itself reflexly against being overwhelmed. But these very defences whose aim is to protect the immature Ego, defeat their own end, if they persist, by interfering with its development. So they keep the Ego weak, Given, then, that, in so far as a patient is neurotic, his Ego is bound to be weak, what has to be determined is whether or not, with the help of treatment by analysis, he would be capable of doing two things.

One of these has to do with his sense of reality, potential if not yet actual. Would he be capable, not merely at a rational level, but deep down too, of seeing through the fixed preconceptions, based on early experience interpreted childishly and so, often, extremely unrealistically, depressingly and terrifyingly, by which his attitude towards himself and the outside world is still conditioned? Would he be capable of distinguishing fact from fantasy, of discriminating his present circumstances from those in which he actually was, or believed himself to be, in his childhood? Recovery, in one of its aspects, depends on his being able to do these things. If he can do them this will release him from his stereotyped, compulsive, neurotic behaviour patterns which are conditioned by his persisting preoccupation with the past, especially from the profound grudges, the rooted mistrust, the intense guilt and the basic despair which weigh so heavily on all neurotic personalities.

This will do much to improve the love-rage-fear balance and the balance between hope and despair and between contact-seeking and withdrawal, since contact will become safer and more likely to offer satisfaction. And as the submerged, arrested part of himself, which was cut off from life, becomes better able to be aware of what is really happening it will be in a position at last to learn by experience, and so to be released from its fixations, complete its growing up and become integrated with the rest of the self.

Besides awareness the other Ego-function which must be taken into account is concerned with integration, co-ordination, growth and mastery. From this point of view the patient's recovery will depend on his being able to do without the reflex defences by which he has been protecting himself from being at the mercy of his own inner urges and the outside world, not, of course, by exercising no control at all, for that would land him in chaos, but by outgrowing them and replacing them by self-direction. Functioning at this Ego-level the personality acts as a whole in a co-ordinated, purposeful way, adapting itself, in the light of

awareness and judgment, and harmonizing the conflicting forces inside itself, where this is possible, or, when it is not, choosing among them, giving right of way to some and blocking others which conflict with those which it has chosen.

This Ego-functioning differs from the other kind of blind, stereotyped reaction in the same way as voluntary differs from compulsive, healthy from neurotic, intelligent from instinctive, purposeful from automatic behaviour. If it is true to say that there is something distinctively human about learning by experience, purposeful self-direction and deliberate choice guided by intelligence, all of which we have been regarding as the functions of a strong Ego, then perhaps we might speculate that one goal at which evolution appears to be aiming is the development of the Ego. Certainly it seems to be the aim of growth towards maturity in the individual human being.

If psychological investigations into the functioning of the personality and neurological investigations into the functioning of the brain are converging over this central problem a point may before long be reached at which it would be possible to link up what organic medicine is discovering about integration at the higher levels of the nervous system and what psychoanalysis is discovering about the development of the Ego.

Dr. William Sargant and Dr. Eliot Slater: In psychiatry to-day we have reached a curious state of affairs in which we are aware of the value of a number of treatments but do not understand their indications. We can, indeed, get a considerable amount of guidance from established systems of diagnosis and classification. The schizophrenic patient, for instance, cannot be treated on exactly the same principles as the neurotic. But the indications provided in this way are not by themselves sufficient, and are actually neglected by some clinicians. We should be able to add to them more refined methods of assessing therapeutic needs. This is, unfortunately, not common practice; and what we see instead is the application of rule of thumb and personal bias. Among our number are those who consider that all sorts of disorders are best treated by psychotherapy; and there are others who submit almost every variety of patient under their care to electroshock, or to electronarcosis, or to narco-analysis, or to some other pet method. This is a state of affairs which cannot be tolerated for long. Somehow or other we must learn to say not only that such and such a patient might well be treated by method A, but also that methods B, C and D are inappropriate. Before we can do this with confidence, we must accumulate a very much larger amount of information than we have at present about success and failure with different methods in different conditions. Reports on the results of physical methods appear from time to time, but we would like to appeal to our psychotherapeutic and psychoanalytic colleagues to come forward with their statistical and clinical results. From the Annual Report of the Institute of Psychoanalysis, we see that during the year 1948–49, 51 cases of obsessional reaction were recommended for psychoanalysis, and only 3 for treatment by other methods. We can be sure of this. There is no psychological, just as there is no physical, cure-all. If psychoanalysis, or any other specific psychotherapy, is a really powerful method of treatment in one case, then there will be another case in which it is useless or dangerous. The various psychotherapies must have their indications and contra-indications; but what they are we yet wait to be informed.

In obsessional neurosis therapeutic confusion is at least as bad as in any other field. Obsessional patients are psychotherapized, psychoanalysed, shocked, insulinized, drugged into sleep, and leucotomized. How often are these methods successful, and in what sort of patients? Obsessional neurosis offers a particularly difficult therapeutic problem. The obsessional constitution is tough, solid, obstinate material. The patient can be battered by electroshock into a confusional dysmnesic state, and on recovery show all his old behaviour patterns unaltered, with added impairment. With insulin treatment he sometimes feels a little better when in a semisoporose state but afterwards feels worse. Under sleep treatment, the drugs hardly alter his symptoms, and instead of relapsing peacefully into sleep he is likely to become confused. Leucotomy will often have a beneficial effect on his anxiety and tension, and despite that he will maintain the old compulsive thoughts. Can one cure obsessionals by letting them talk? We have seen one obsessional boy who had had psychoanalysis and had recovered, though he had relapsed before he came to us; and the connection between treatment and recovery we could hardly regard as established. Another obsessional patient reached us after spending during a long illness four years with one very distinguished analyst, one year at the Institute, and five years with another analyst—and was still spending many hours every night in the lavatory.

In this paper we shall give a short account of our experience with various physical methods in the treatment of obsessional neurosis. This experience has been sufficient to clear the ground for us, and to provide definite contra-indications to at least some of the methods in common use.

Sleep treatment is only occasionally of any value. Large doses of drugs are often needed as the patient is afraid to sleep and will not relax. After drug-withdrawal there is an enhanced

risk of confusional states which may even land the patient temporarily in a mental hospital. Well-established obsessional behaviour patterns are not touched. Sometimes, however, one will find an obsessional patient who has succeeded in keeping his symptoms within reasonable bounds for a long time, but as a result of recent emotional pressures has become anxious, worried and exhausted, so that his old symptoms impose an intolerable burden. Such a patient may be helped by sleep, which will relieve the anxiety, and enable him to re-adjust in the old pattern.

Modified insulin treatment rarely helps much. Its effects on the obsessional may be paradoxical. Janet pointed out many years ago that improving the physique of psychasthenics often only increased the strength of their conflicts. We have seen obsessional prisoners-of-war who were relieved of their symptoms when semistarvation had caused a severe loss of weight; and we have observed vomiting and physical debilitation in patients under our care cause a temporary remission of symptoms. On the other hand as, under modified insulin treatment, the physique improved, tension became greater, in marked contrast to the anxiety-hysteric who in parallel circumstances rapidly improves. The benefit derived from physically lowering treatment may be the basis of such methods of treatment as starvation cures, vegetarianism, &c. One of our patients put on a rice diet showed a considerable lowering of tension. Part of the psychoanalytic theory of obsessional states is that libido is wrongly directed. We know that stilbœstrol in the male reduces sex tension. It is our experience that it may reduce tension generally, if given in doses of 5–15 mg. a day. If we may be permitted to speak in libidinous terms, we might say that under this treatment the lowering of the level of libido allows it to be diverted on to less narcissistic objects; in plainer language, the patient complains less of his symptoms. Interesting results with stilbœstrol have also been seen in selected male patients, both schizophrenic and obsessional, in whom tension and obsessive rumination were outstanding symptoms.

We have no recollection of any obsessional patient, who was not schizophrenic, being benefited by insulin coma treatment. Admittedly we have treated very few such patients in this way ourselves. But we have had no success at all, and if others have tried it they have not reported improvements. Even the combination of electroshock and insulin coma has proved in our hands unavailing.

Treatment by electroshock requires more detailed discussion. An obsessional neurosis is not the only illness to which the obsessional constitution is heir. It is also liable to a form of endogenous depression which shows itself very often as one of involutional type. With these states, even if they occur in the earlier rather than in the involutional years, electroshock will generally prove of the greatest value. The clinical signs of a definite and lasting depression will hardly be mistaken. It is above all when retardation is in the centre of the picture that good results will be obtained. Generally speaking the patient who sleeps well, even if he is apparently depressed, does not respond to E.C.T. The best results are obtained with those who suffer from an early morning wakefulness, and are more depressed in the morning than in the evening. When this diurnal rhythm is reversed, there is a danger that shock treatment will make the patient worse rather than better. In any case the good effects of shock treatment will be limited to the relief of the depression. One cannot expect that a pre-existing rigidity of temperament, or a tendency to compulsive rumination, will be favourably influenced.

Compulsive symptoms are by no means rare in depressions occurring in persons of non-obsessional personality. They are often monosymptomatic, nearly always confined to a limited field, and have only appeared with or after the onset of the depression itself. This syndrome must be carefully distinguished from obsessional neurosis; for compulsive symptoms of this secondary kind nearly always remit with recovery from the depression which was their primary cause.

The affect which is characteristic of an obsessional state is that of tension. We have never known this to be relieved by electroshock, not even after an intensive course which has reduced the patient to a state of confusion with bed-wetting. The notion that E.C.T. is a half-way stage towards leucotomy is fundamentally false. The two are poles apart in their physiological effects. Put in its simplest form, E.C.T. is a treatment for retardation and the depressive affect; leucotomy is a treatment for anxiety and tension. Apparent paradoxes can be resolved. The agitated melancholic is usually tense, and yet responds to E.C.T. This tension, however, is secondary to the depression and disappears as the primary affective change yields to treatment. Furthermore, the tension is of a different quality to that seen in the anxious and obsessional patient. One will not see, in the melancholic, the same signs of sympathetic overactivity. When placed on the couch to take treatment, neither pulse nor breathing may alter. On the other hand, some involutional melancholics make only a partial remission with electroshock. They are generally of anxious or obsessional personality, and the failure of treatment is accounted for by the persistence of these traits in enhanced form while the depression has lifted. These are the depressive patients who eventually may need a leucotomy.

The hopes that intensive E.C.T. would benefit obsessionals have, in our experience, not been borne out. Even in ordinary doses it usually makes the obsessional patient worse, by increasing his anxiety, and he may remain worse for years. If he is already depersonalized, this symptom too is unrelieved or exacerbated; and if he is not, E.C.T. may cause the symptom to appear. If it does appear, it is itself likely to persist for a very long time.

E.C.T. is a quick, easy and convenient method of treatment. There are few centres now where it is not available. There is a strong temptation to "have a go". It is one thing to try a few electroshocks, carefully watching for results, in case one has missed a depression; and quite another to submit an obsessional to one of those prolonged courses which are a curse on present-day treatment. Least of all is it justifiable to submit the obsessional patient to a long course of E.C.T. simply because one already has leucotomy in mind. The undesirable after-effects of E.C.T. are often experienced as subjectively disturbing when a later leucotomy has benefited other symptoms; and we have observed several patients with slight memory disturbances, attributable to E.C.T., which though not increased by leucotomy made the post-operative adjustments more difficult.

We have already referred to the toughness of the obsessional constitution, and the incapacity of the obsessional patient to relax. Drug abreactive treatments, accordingly, have entirely different effects with obsessional and hysterical patients. The fluidity of nervous integration in the hysteric permits him to abreact emotions, and to regain normal integration with benefit to his symptoms. The obsessional patient behaves differently. He will not let himself go. As dissociation threatens, all his fears mount to a peak. He is afraid of going mad; and indeed he may go mad, that is pass into a confusional state, if pressed too far. Similarly, Meduna's carbon-dioxide treatment has in our hands always failed with obsessionals and if persisted with, has usually made them worse. This is a point to be specially borne in mind by those who have been encouraged by successes with this new method in traumatic hysteria.

The foundation of psychoanalysis was laid down when Breuer and Freud treated a hysterical patient by abreaction. Freud later abandoned this method for free association. It is possible he did so because of poor results with patients of obsessional type. A drug technique which more nearly resembles free association than abreaction can be helpful with some obsessionals, in our experience and that of our colleague Dr. Shorvon; and Delay and others in France have noticed the same thing. This is to give not a narcotic drug but methedrine, which is an excitant. Janet, to whom we owe most of our basic knowledge of obsessional states, stressed the need for the re-excitation of the obsessional. Under methedrine, the patient does not dissociate, but is temporarily released from his preoccupation with obsessional symptoms and is able to pour out a stream of talk touching on more general fears and ruminations, with at least occasional and temporary relief. We are not prepared to speak of long-term results. Why this should be so is not easy to explain, and we speculate very hesitantly. Löwenfeld has spoken of anxiety always being discharged through the traumatic focus. If one can consider that there is a local disturbance of brain function in an obsessional state, then methedrine may allow, through its general excitatory effect, of other pathways between thalamus and cortex being activated. In more general terms the excitation of alternative emotional pathways may be the basis both of spontaneous remission and successful psychotherapy. As one example, if the attention of the obsessional is diverted from his symptomatic ruminations on to recollections of infantile sexuality, as is attempted by analysis, he may well be helped. Infantile sexuality does not, however, have to be the theme. We have heard of one obsessional patient who was cured of a syphilophobia by an experimentally minded venereologist telling him that he need have no fear of G.P.I., but his heart was in a very bad way. He forgot all his old fears in his anxiety over the new one. The old pattern had been disrupted, and the new anxiety, so recently imposed, could be dealt with fairly easily by simple methods of reassurance.

We come, last, to the subject of leucotomy. At one time, we were inclined to think that we got better results with leucotomy in obsessional states than in any other condition for which the operation was used. Certainly nearly all our early cases, which were handpicked out of many thousands of neurotic patients who went through Sutton Emergency Hospital, did remarkably well. Later subjects have not always done so well, and if we have had excellent results we have also had patients who derived no benefit. This is, perhaps, in part due to the fact that in the course of time the standard operation has been modified and has tended to become a milder one. It may also be that our earlier cases were more intensively studied. The development in operative technique, though it may have caused us some disappointments, will, no doubt, in time lead to the discovery of an operation which will produce the maximum relief with minimum damage to the personality. As things are at present, one cannot expect that obsessional ruminations will entirely disappear without signs of a flattening of the personality; but a lesser degree of damage may abolish the tension they cause. The patient improves because his symptoms cease to excite the same emotional response, and with lack of continued emotional reinforcement become of little importance.

Altogether our combined experience over the past eight years amounts to about 40 cases in which an obsessional component played a dominant part in the disability, and who have been leucotomized. Out of our 22 earliest ones, 9 made a recovery which we are strongly tempted to call 100%, only 3 derived no benefit and the remainder all made substantial improvements of different degrees. All these patients were chronically incapacitated, and were originally considered intractable. They have been followed from the year 1942 when the first of them was operated.

Our best results have been obtained with the patients who had the best premorbid personality, and especially those who, when their illness came on, tried their best to keep going in a socially normal way. Patients who had gone from clinic to clinic in the search for help responded favourably. On the other hand, signs of complacency and anergia of personality are unfavourable prognostically. We have found that comparatively late onset of symptoms, say in early adult life, is more favourable than an onset in childhood. Obsessional states which are monosymptomatic, or with strict limitation of the field of abnormal experiences, respond very well. It has been our experience that states where symptoms are shown predominantly in the sensory and subjective fields react to operation much better than those in which there is an abundance of motor symptoms. Several of our patients who failed to improve after a first operation have done extremely well after a second. In these cases, either the first operation was deliberately modified, e.g. a lower-pole operation only, or there has been an absence of post-operative psychological effects indicating that at operation very little if any damage had been done. However, in considering patients for a second operation, we prefer those who had a temporary improvement, even if followed by relapse, to those who did not change at all. We have not found that age is any bar to treatment. One of our patients, a woman of 69 with a duration of illness of twenty years, is now very well indeed at the age of 72; and two other male patients of over 70 have done extremely well. But if age is not a bar, youth probably is. Young patients do not usually do well: and we would deplore the application of the operation to children, until we have much more knowledge and understanding.

In this connexion there is one risk to which we should like to draw attention. A few of our patients after operation have passed into a characteristic schizophrenic state. We do not wish to suggest that leucotomy caused this development, although that possibility cannot be entirely excluded. It does seem possible that leucotomy may loosen the integration of the personality and deprive it of defences, after which a pre-existing schizophrenic process can make more rapid headway. The patients who showed this unfavourable change also all showed some atypical clinical features in their obsessional neurosis. One of them was hearing auditory hallucinations before the operation, but could only bring herself to admit them afterwards. Another patient had obsessional ruminations about the size of his head, which retrospectively in the light of later knowledge had a quality of the delusional. We would therefore suggest considerable caution in recommending the operation, especially in persons under the age of 30, and above all if there is anything clinically atypical.

We must remember that there are many problems still unsolved. Every year brings us some new advance, and where, in an individual case, we are on unsure ground we can hold our hands a little. We have no evidence that the prognosis is worsened by waiting even a year. None of our best patients has in the end suffered from delay, and the patient who goes downhill rapidly is very likely a schizophrenic. This is without prejudice to social considerations which must be allowed due weight; the man of good personality, for instance, will remain intact, but he may be in danger of losing his job if nothing is done. As Lewis has shown, spontaneous remission is not infrequent, and may occur even after prolonged periods of illness. One of our patients had a previous illness of seven years' duration, a remission and several years of comparative health, before an eventual relapse reduced her to a state of prolonged misery and necessitated operation. But if caution is indicated, so also is reasonable courage. If we are faced with a patient whose obsessional symptoms are characteristic, of prolonged duration and in one way or another incapacitating, then leucotomy is the treatment of choice.

Dr. W. Clifford M. Scott said that he considered Dr. Stephen's summary of the already published psychoanalytic literature concerning the treatment of obsessional states by psychoanalysis was quite adequate. Individual psychoanalysts knew more about their successes than about their failures and he made a plea that psychiatrists treating the failures of psychoanalysts should let the psychoanalysts know the outcome.

Dr. Scott was certain that the Directors of the London Clinic of Psycho-Analysis would be very grateful for such help in assessing results. He hoped that eventually enough data would be collected by the co-operative efforts of many psychoanalysts to enable the different factors contributing to the success or failure of any given psychoanalytic treatment to become clearer.

Section of Ophthalmology

President—M. L. HINE, M.D., F.R.C.S.

[*March* 10, 1950, *continued*]

MEETING HELD AT THE MOORFIELDS BRANCH OF MOORFIELDS, WESTMINSTER, AND CENTRAL EYE HOSPITAL, LONDON

Iridoschisis.—P. McG. MOFFATT, F.R.C.S.

W. H., male, aged 59.

No relevant previous history except that he did a lot of boxing during first World War and received several blows on and about the eyes and after one particularly severe blow in 1916, he states that the appearance of the right eye was altered but he still retained useful vision.

No relevant family history.

First attended Royal Westminster Hospital in 1943 for asthenopia and a disturbance of the pigment of the right eye was noted.

Corrected vision was 6/6 R.E., 6/9 L.E. The left eye showed early lens changes.

Attended 1948 with mature cataract of left eye and post-central opacities of the right eye. The left lens was removed in 1948.

In January 1949 the right cataract was mature and the left had 6/6 vision after capsulotomy.

At this time fibres from the periphery of the iris were seen to be adherent to the posterior surface of the cornea in both eyes.

He has now been admitted for right extraction and the condition was found to have progressed to its present state, which is shown in the photographs.

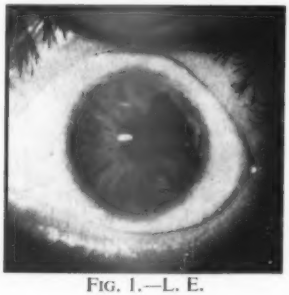


FIG. 1.—L. E.

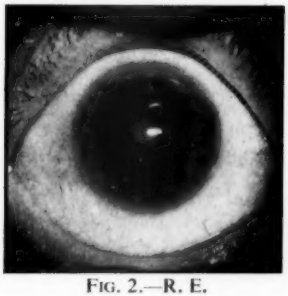


FIG. 2.—R. E.

[*May* 11, 1950]

Congenital Retinal Fold, in Association with Pseudopapillitis.—P. D. TREVOR-ROPER, F.R.C.S.

A man, aged 28, had been referred by his optician as his sight could not be improved beyond 6/24. He had apparently never been able to read small print. About twelve years previously the patient had been seen by a doctor in Middlesbrough, who wrote that he remembered the abnormal discs and the amblyopia which he could not improve, but he had not then noticed any abnormal retinal condition. In 1946 the patient was referred to this doctor again, and the retinal fold was then also noted. The following abnormal signs were now evident:

(1) Both discs were very prominent, congested and with an ill-defined margin.

(2) There was a sheet of retina with fine tortuous blood vessels lying in front of the normal retina in the lower quadrant. This was irregular but could be described as a sector-shaped sheet, directed towards the disc (although falling short of it), and with a very large bite taken out of it (Fig. 1). The normal retina appeared to continue underneath it, the different sets of blood vessels showing an obvious parallax.



FIG. 1.—L. E. 22.3.50.

(3) Both retinæ showed small scattered foci of intense choroidal sclerosis.

(4) Apart from slight bilateral superior oblique overaction, the eyes appeared otherwise normal, but the vision corrected only to 6/24 in each with a relatively small hypermetropic and astigmatic error. There was no blind spot enlargement, and the only field change was a slight peripheral restriction in the left field exactly corresponding to the retinal fold.

The speaker thought that the case must be one of a congenital retinal septum or fold. These could occur at any site, and normally ran from the disc, fanning out to reach the ora serrata and posterior surface of the lens; in this instance it was incomplete.

Such cases are said to result from an abnormality of the hyaloid vascular system, with persistent adherence of the primary vitreous to retina so that it lifts up a fold of retina, usually leaving tags of the hyaloid remnants and occasionally patches of gliosis adherent to its edge, although these are often visible only microscopically. The fold indeed resembled a shallow detachment, but the presence of subjacent retinal blood vessels would seem to rule this out.

The changes in the optic discs seemed more gross than could be explained as a physiological variation in a mild hypermetrope, and he suggested that they were evidence of the gliosis that was such a common feature along the course of the distracted hyaloid system with retinal folds, although here it was localized to the disc, whereas the fold itself stopped short of it.

It seemed improbable that the retinal abnormality could have been overlooked twelve years ago, yet in eyes already showing congenital defects, discs and amblyopia, he was reluctant to surmise a recent origin of the fold in spite of its unusual features.

Mr. Eugene Wolff suggested that this was a choroiditis. At one time there was inflammation involving the choriocapillaris, an exudate passed through the retina and into the vitreous, and the fold was the organization of that exudate.

Mr. E. F. King was of the contrary opinion to Mr. Wolff. He did not think that it was organized exudate.

[*June* 8, 1950]

DISCUSSION ON GONIOSCOPY

Mr. A. J. B. Goldsmith: *Technique and normal appearances.*—It is surprising that gonioscopy as a method of clinical examination is of reputable antiquity, having already achieved its golden jubilee. The first examination of the angle of the anterior chamber was made as long ago as 1898 by Trantas, who, using pressure on the limbus and direct and indirect ophthalmoscopy, was able to obtain views of the angle in about 25% of cases. Little notice was taken of his observations at the time as the technique was unsatisfactory, but in 1914 Salzmann used keratoconus contact lenses to make the examination easier and to increase the extent of the angle accessible to view. Later still, in 1920, Koeppe devised a special contact lens with which the slit lamp and a monocular microscope could be used, and after the middle 1920s the practice of gonioscopy was enthusiastically pursued and written upon by many ophthalmologists among whom one may mention Troncoso, Castroviejo and Barkan in America, Busacca in South America and Goldmann and François in Europe. In this country, essentially conservative as we are in spite of our political complexion, it is only in recent years that even a small proportion of oculists have familiarized themselves with its technique. I think probably so far as glaucoma is concerned we have been right. Gonioscopy does not by any means give all the answers to the cause of glaucoma, nor even as to the best means of treating it. Clinically gonioscopy is of considerable interest in following the course of events in the angle of the anterior chamber in glaucoma, and in examining various pathological conditions such as new growths and foreign bodies in that region. It is perhaps of even greater interest in illuminating the technical faults which may be responsible for the failure of anti-glaucomatous operations. On the research side, gonioscopy is providing information which, taken on its own, is quite useless, even fallacious, but which is fitting into our conception of the nature of glaucoma.

In these opening papers I propose to discuss the technique of gonioscopy and the appearance of the normal angle, while Mr. Hobbs will collate the observations which have been made in the glaucoma clinic at the Institute of Ophthalmology, and mention the work of other observers.

Technique.—The earliest observations were made without any special instruments. The use of a deeply curved contact lens made things considerably easier. The angle of the anterior chamber is accessible to direct view either not at all or with much difficulty since the scleral overlap makes direct view from the zenith impossible while the view from the opposite limbal region has to be made so obliquely that the front surface of the iris may well prevent the recess of the angle from being seen. The essential principle of any lens used for gonioscopy is that it shall so modify the optical conditions as to permit of direct observation of the angular recess along a line bisecting the angle between the anterior surface of the iris and the posterior surface of the cornea. Such a lens together with suitable illuminating and observing systems constitutes the necessary apparatus.

Of the various lenses used Koeppe's type and Troncoso's modification of it are deeply curved glass lenses. The space between the lens and the cornea is filled with normal saline and the patient is best examined lying down with some instrument such as the Troncoso gonioscope in which the illuminating and observing systems are combined. This technique necessitates a peripatetic examination if one wishes to see all parts of the angle. Goldmann's lens, which we use at the Institute, offers considerable advantages. It can be used with the patient sitting up at the slit lamp; any slit lamp serves for examination, the best types being perhaps those with a one-hand manipulation of the controls such as the Haag-Streit or Aimark instruments, as these leave the other hand free to support the gonioscope lens and to rotate it so as to bring all parts of the angle into view.

This lens is easy to use. The patient's eye is anæsthetized with one drop of 1% pantocaine solution; the lens is filled with normal saline and inserted between the lids while the patient's head is bent forwards. The avoidance of air bubbles is a matter of practice. Once the lens has been inserted the patient's chin is placed in the chin rest of the slit lamp which has already been adjusted. Speaking as a subject I can say that the examination is entirely free from any discomfort and the only complication we have experienced in the course of several hundred examinations was a minor corneal abrasion. For antisepsis we keep the lenses in between examinations in a 1% solution of C.T.A.B., washing them in running tap water before use.

The interpretation of the topography of the angle is easy if one can visualize the normal histology of the region. The main landmarks which form a series of concentric circles are (Fig. 1) from behind forwards :

(P) The pupil margin.
(I) Anterior surface of iris.
(CB) Antero-medial surface of ciliary body.
(Sp) The scleral spur (posterior annular line).
(Tr) The trabeculæ covering the canal of Schlemm.
(Schw) Schwalbe's ring (anterior annular line).
(S) The concave inner dome of the cornea.

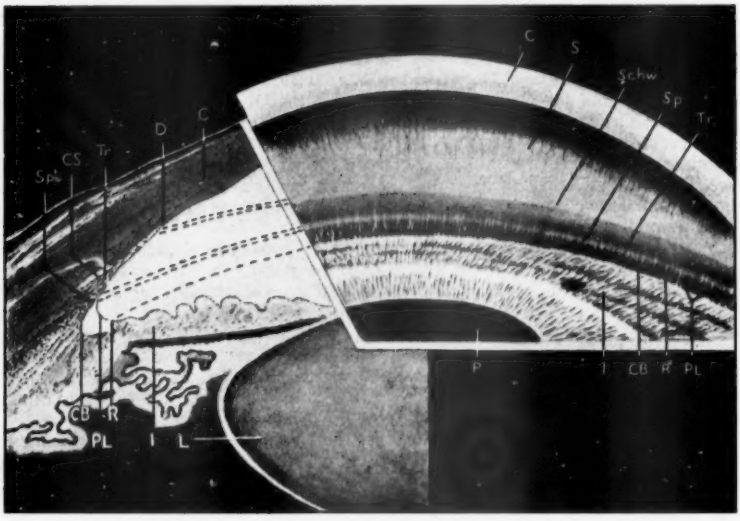


FIG. 1.—Angle of the anterior chamber of a normal eye seen through Koeppe's contact glass and gonioscope. Semi-schematic picture showing correspondence of different structures with those of a microscopic section. P: Pupil. I: Iris. R: Ciliary border of the iris. CB: Ciliary body. Sp: Scleral spur. PL: Pectinate ligament. Tr: Sclerocorneal trabeculæ covering Schlemm's canal, CS. Schw: Schwalbe's line. S: Inner dome of the cornea with the rami recurrenti vessels of the corneal limbus. D: End of Descemet's membrane. C: Cornea. L: Lens.

The limits of the angle, so called, are usually taken as on the corneal side, Schwalbe's ring, and on the iris side a point opposite to Schwalbe's ring, a point which sometimes coincides with the most peripherally situated line of contraction folds of the iris, and it is the structures within the angle which are of especial interest in glaucoma.

The iris, on the surface of which flecks of pigment may be seen, ends in a slightly wavy line, its ciliary edge. Beyond this, and at a slightly deeper level is a curved band, always darker in colour than the iris and of variable width. This band is formed by the anteromedial surface of the ciliary body as it passes forwards to its insertion in the scleral spur. In blue eyes this band is yellow or orange; in brown eyes it is always darker than the iris itself. In myopic eyes the iris is inserted farther back on the ciliary body so that the ciliary band is wider than in normal or hypermetropic eyes. The ciliary band forms the lateral wall of the angle, which is, therefore, strictly speaking, not an angle at all but a curved recess of variable width.

Immediately cornealwards to the ciliary band is the posterior annular line, which is sometimes visible, but whose presence is usually inferred from its relation to the ciliary body; it represents the scleral spur to which the ciliary body is attached. Schwalbe's ring, which lies some 0·7 mm. further forwards, may appear to project into the anterior chamber; it represents the end of Descemet's membrane (D, Fig. 1) and appears as a quite definite white ring. Between these two rings of the scleral spur and the end of Descemet's membrane lie the corneoscleral trabeculæ which appear blue or grey in young eyes, and yellow or light brown in older persons. Schlemm's canal, which I shall return to later, lies under the outer one-third of this trabecular band. Anterior to Schwalbe's ring lies the inner convex dome of the cornea. The cornea always looks yellowish in optical section and through it can often be seen some of the limbal vessels.

Now leaving these concentric rings we turn to other structures. The first of these are the pectinate fibres (PL in Fig. 1) of the iris, extensions of the iris mesoderm which continue beyond its root over the ciliary body band and for a variable distance on to the trabecular band. They appear as ridges on the otherwise smooth surface of the ciliary body and their number, size and thickness vary considerably (Fig. 2). They have to be distinguished from

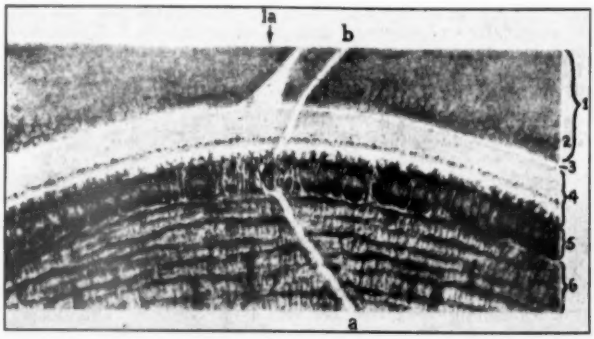


FIG. 2.—Normal wide angle of the anterior chamber as seen in the mirror of Goldmann's contact glass (la lower part). Man aged 39. × 30. Narrow beam of the slit lamp microscope, a, over the iris, b, over the cornea. Between them the beam follows the concave surface of the sinus. 1: Cornea. 2: Network of limbus vessels seen from behind. 3: Anterior border ring of Schwalbe. 4: Trabecula sclerocornealis or meshwork of the angle with a line of pigment at its lower part directly over the place of Schlemm's canal. Underneath this pigment line appears a narrow white line, the scleral spur. 5: Anterior surface of the ciliary body over which plays a wide, dim, light reflex. In front of the ciliary body run the vertical fibres of the ligamentum pectinatum (scleral trabeculæ) which, springing from the iris edge, cross the sinus and end apparently below the scleral spur, although in reality they continue over the trabeculæ. 6: Iris. (After Goldmann.)

peripheral anterior synechiæ of the iris; this is usually fairly easy as they are much thinner, are present around most of the circumference of the angle, and never extend farther forwards than Schwalbe's ring.

Next, Schlemm's canal; this is visible only if it contains blood when it appears as an ill-defined pink streak lying under the outer third of the trabecular band (Fig. 3). Using the

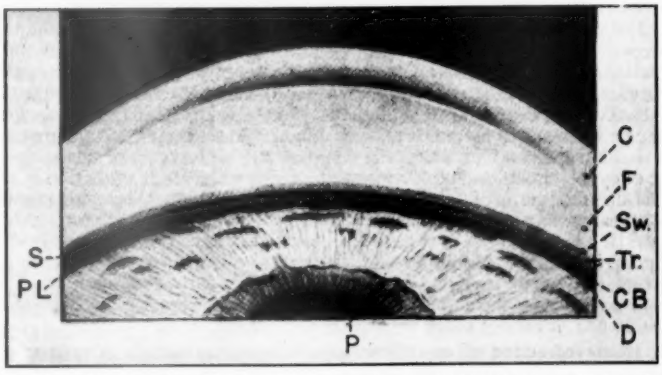


FIG. 3.—Angle of the anterior chamber in a normal eye with light-coloured iris. S: Schlemm's canal filled with blood and appearing through the trabeculæ, Tr, as a narrow dark band. F: Inner surface of the cornea. C: Cornea. Sw: Schwalbe's line. CB: Ciliary body band. D: Ciliary border of iris (last roll). PL: Pectinate ligament fibres.

(Figs. 1, 2 and 3 are reproduced from Troncoso's "Treatise on Gonioscopy", F. A. Davis Company, Philadelphia.)

standard Goldmann lens it is only rarely visible, but Mr. Hobbs has made a modification of this lens in which a flange exerts a pressure on the episcleral tissues some 4 to 5 mm. from the limbus producing venous congestion.

With this lens we have examined the eyes of twelve normal subjects whose ages range from 25 to 67, and have seen the canal fill with blood, partially or completely, in all cases. Blood appears when the goniolens is applied with light pressure, and firmer pressure causes the canal to blanch, an effect which could also be produced by withdrawing the lens gently against the suction with which it adheres to the globe. Congestion of the episcleral tissues is apparent from the ring of œdematous conjunctiva seen on removing the instrument; this subsides in ten to twenty minutes. In some cases further evidence of a rapid return to normality could be seen in the early restratification of previously noted aqueous veins. It was felt therefore that the danger of producing congestion dangerous to glaucomatous eyes was slight, and tonometry before and after examination supports this view; a maximal rise of 6 mm. Schiötz was seen in one patient only, the majority showing an alteration, plus or minus, of less than 2 mm.

The entry of blood into the canal in normal eyes appears therefore to depend on the relative intra-ocular and episcleral venous pressures, and it seems from recent work at the Institute that the same factor operates in glaucoma and that there is no evidence of a blockage between the canal of Schlemm and the aqueous veins.

We have, in a few patients, seen a reflux of blood from the filled canal of Schlemm into the anterior chamber. This blood has appeared at one or more points, usually at the upper part of the angle, slowly trickling down over the surface of the iris. This observation may link up with the canals of Sonderman which have been described in recent years, but we have not seen it sufficiently often to draw any conclusions, nor, so far, have we had the opportunity of repeating the observations in the same patients.

Pigmentation of the angle.—The trabecular band is darker in colour in older subjects. This pigmentation, which may be marked in young patients after an attack of iridocyclitis, appears in general to be related to the age of the subject. It is always more marked below, probably owing to the action of gravity, and the pigment is derived from the breakdown of pigmented epithelial cells and chromatophores. It has been argued that the deposit of pigment in the trabecular spaces is one of the causes of glaucoma, but this is quite definitely not the case and pigmentation is not more marked in glaucoma than in normal subjects of the same age group. Occasionally the deposit is so dense as to make it impossible to see whether or not Schlemm's canal contains blood.

Next I should like to consider the normal physiological variations. The widest angles are seen in cases of aphakia, particularly after intracapsular extraction, and it is in these cases that the various structures of the angle are most easily seen. The angle is wider in myopic than in normal eyes, while in hypermetropic eyes, particularly those with small corneæ and shallow anterior chambers (the type of eye liable to attacks of subacute glaucoma) the angle is often so narrow that it is impossible to see the structure within its recess, and even, in some cases, to be certain whether or not peripheral anterior synechiæ are present.

The effect of drugs on the angle may be studied by gonioscopy. It is perhaps surprising that the effect of miotics is to narrow the angle as, under the action of miotics, and also with accommodation, the ciliary body is displaced forwards, rotating as it were, round its attachment to the ciliary spur. Conversely with atropine, the angle becomes wide, the ciliary body retracting backwards and rotating outwards. These findings may appear incompatible with the known tendency of mydriatics to cause increased tension in certain eyes, particularly those with shallow anterior chambers. I believe that the explanation of this antinomy is that, in this type of eye, even although the sinus itself may be widened by the action of a mydriatic, the bunched-up mesoderm of the iris, when the pupil is dilated, becomes apposed to the posterior corneal surface, and blocks access to the angular sinus, and therefore to the trabecular spaces. It is in this type of eye, subject to attacks of subacute glaucoma with haloes and slight pain, that the use of miotics is an efficient prophylactic, often preventing the occurrence of attacks for many years, and it is in this type of case that the purely mechanical effect of eserine in contracting the pupil affords an adequate explanation of its good effect—if the iris is stretched, it cannot block up access to the angle.

In other cases the action of eserine, if any, in lowering tension is probably due more to its effect on the capillary circulation, and on the descending pressure gradient

$$\left(\text{arterioles—capillaries} < \begin{matrix}\text{intra-ocular venules} \\ \text{aqueous—canal of Schlemm—aqueous veins—episcleral veins}\end{matrix}\right)$$

than to its effect in contracting the pupils and affecting the permeability of the trabeculæ.

Finally, I think there are no signs in the angle which will help to establish the diagnosis of glaucoma in an early doubtful case. In most cases of non-congestive glaucoma the angle

shows no definitely abnormal changes; pigmentation is normal with advancing age, and even in capsular exfoliation it is quite impossible to say from the amount of capsular debris deposited in the angle what the intra-ocular pressure is likely to be. In cases with shallow chambers and narrow angles one can assess what degree of embarrassment of the angle is likely to be caused by dilating the pupil, but I do not think one can assess what is the patient's liability to attacks of acute or subacute glaucoma, nor how long he is likely to be controlled by miotics. Peripheral anterior synechiæ of the iris may develop after attacks of iritis, or in iridoschisis, and if extensive they may result in a rise of intra-ocular pressure, but here again it is quite impossible to say, for example, that if 50 or 75% of the angle is blocked, the tension will be raised, since after cyclitis the tension may be raised in the absence of synechiæ and may be normal even when the greater part of the angle is occluded.

If peripheral anterior synechiæ are seen in cases of primary glaucoma, they are evidence of previous congestive attacks, or an operation.

(For References *see* p. 1024)

Mr. H. E. Hobbs: *Clinical observations.*—It must be evident at once that, in so far as gonioscopy offers greater ease in visualizing the angle of the anterior chamber *in vivo*, its scope must cover the whole range of disease affecting this part of the eye. In a few of these lesions the examination has been able to provide information which may be said to be new, in the sense that it has not been available, *in vivo*, by other methods of examination. In the main, however, gonioscopy offers an amplification of detail and a more complete visualization of appearances which are already, to a large extent, familiar.

Foreign bodies in the chamber angle, especially glass ones, provide an example, since in these cases, although there may be a strong suspicion of their presence from the history of injury, the detection of a scar involving the whole thickness of the cornea and recurrent attacks of irritation of the eye, the foreign body may not be able to be seen by direct inspection. I have recently seen such a case, an air-raid casualty, in whose left eye the presence of a piece of glass in the anterior chamber had been suspected but not definitely located until lately. Fig. 1 demonstrates the clarity with which gonioscopic examination reveals the foreign body wedged in the angle.

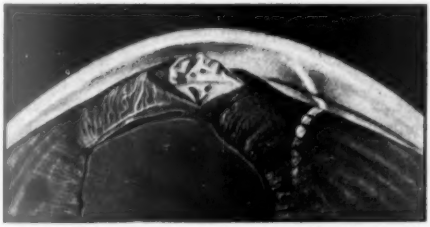


FIG. 1.—Glass foreign body in the chamber angle.

Iris tumours.—The tangential view afforded by the gonioscope in many cases enables one to decide with more certainty whether or not the pigmented area seen on direct inspection forms a nodule raised from the surface of the iris, and how far it extends into the angle. Its proximity to the landmarks of the angle, seen gonioscopically, enable one to assess its progress. Troncoso's illustrations (Figs. 2A and B) show these points well.

Troncoso provides, in his monograph on gonioscopy (1947), a comprehensive review of the scope of the method in assessing the extent and complications of injuries, inflammations and congenital abnormalities at the iridocorneal angle and perhaps the most important of these last arises in the condition of buphthalmos.

Glaucoma.—In glaucoma the detail of the angle has been carefully scrutinized, and as a result of such examinations, again, some new facts have been reported and much has appeared in confirmation of previous clinical impressions. In consequence, new theories have been put forward concerning which agreement is not, as yet, unanimous.

In the inspection of the chamber angle with the gonioscope an estimate of its breadth may be made. Angles classified as narrow are found to be almost constantly associated with congestive attacks, a finding which appears merely to confirm the general impression that this type of glaucoma is found commonly with a shallow anterior chamber. It is of interest, however, to recall the findings of Gradle and Sugar (1940) in a series of cases in which they compared the acuity of the angle with the depth of the anterior chamber. They found that although the occurrence of a shallow anterior chamber in association with a narrow angle

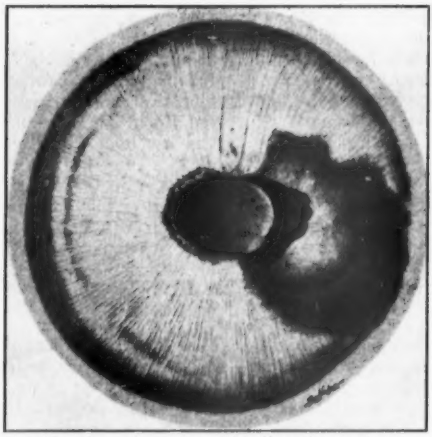


FIG. 2A.—Appearance by direct inspection.

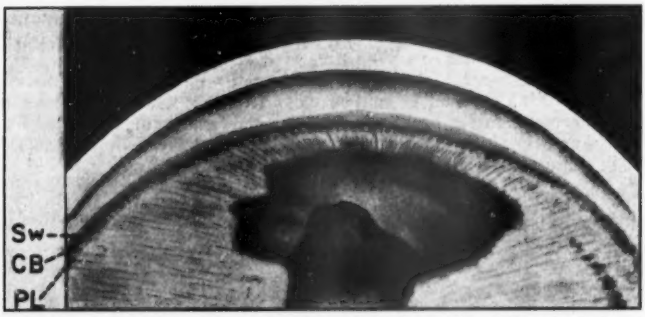


FIG. 2B.—Gonioscopic view. Sw: Schwalbe's line. CB: Ciliary body band. PL: Pectinate fibres.

(FIGS. 2A and B are reproduced from a colour plate in Troncoso's "Treatise on Gonioscopy" F. A. Davis Co., Philadelphia.)

is usual it is by no means constant and state that they regard the appearance of the angle rather than the depth of the anterior chamber as the important factor in determining the onset of congestive attacks. I have myself seen shallow angles in one or two patients, subject to congestive attacks, in whom the depth of the anterior chamber, confirmed by measurement with the Zeiss slit-lamp microscope and Ulbrich drum, appeared of medium or normal depth, and this association is clearly one to be borne in mind in seeking an explanation of the congestive attacks in such cases.

The findings in 85 cases of primary glaucoma examined at the Institute of Ophthalmology may be of interest in this connexion. Of these 45 were regarded, from the presence of cupping of the disc and characteristic field changes, as examples of chronic simple glaucoma; 10 showed these signs, but gave as well a history of minor congestive attacks and 30 were of the congestive type. My colleague, Mr. S. J. H. Miller, has summarized the gonioscopic findings in so far as they relate to the breadth of the angle in this table:

TABLE I.—BREADTH OF ANGLE IN 85 CASES OF PRIMARY GLAUCOMA

Breadth	Group 1 C.S.G. (45)	Group 2 C.S. with M.C.A. (10)	Group 3 Congestive (30)
Narrow	5	4	23
Medium	20	2	2
Broad	17	1	—
Obliterated ..	3	3	5

C.S.G. = Chronic simple glaucoma.
C.S. with M.C.A. = Chronic simple glaucoma with minor congestive attacks.

Here there is evident a very great preponderance of narrow angles in Group 3; the majority of Group 1 show medium or broad angles, although there are here 5 cases with narrow angles and it is tempting to relate these to Group 2 in which there is only one case with a broad angle; and to suggest that it is the—possibly chance—occurrence of a narrow angle in these cases which has encouraged the onset of the congestive attacks in Group 2, and may yet do so in the narrow-angle cases of Group 1. Where the angle is shown as obliterated, peripheral anterior synechiæ were so extensive as to make an estimate of its breadth impossible, and in all of them an operation had been performed, so that one can hardly relate this state of the angle to the type of glaucoma alone.

Closure of the angle by the apposition of the iris is clearly more likely when the angle is narrow; however, that the formation of adhesions between the root of the iris and the corneoscleral trabecula is the result rather than the cause of glaucoma was first observed by Salzmann in 1915 in a case of secondary glaucoma and Troncoso later emphasized repeatedly (1925, 1933, 1935) that the same is true in all types of glaucoma. Peripheral anterior synechiæ are recognized fairly easily when the landmarks of the angle can be identified and are seen as adhesions between the iris and the trabecula or cornea forming its outer wall. When they are of limited extent there is little doubt of their presence; but when, as frequently occurs, they occupy a large part of the field, and especially when the angle is very narrow, the distinction between firm synechiæ and iris merely apposed or apparently apposed to the outer wall of the angle is more difficult. Here the advantages of a binocular technique, employing a slit-lamp microscope, are of the greatest value; the contour of the narrow beam, seen stereoscopically, permits one to make a decision in most cases and a further feature of value in extensive synechiæ is the appearance at the point of adhesion of a fine line of pigment which appears to be that of the posterior iris layer.

Among the 40 cases from the Glaucoma Clinic in which congestive attacks had occurred were 36 affected eyes which had responded to medical treatment alone, 32 of these 36 eyes had been subject to minor congestive attacks for periods varying from five months to six years and in one only were synechiæ seen, covering 5% of the angle. In two other eyes narrowness of the angle made a definite decision impossible. The remaining two eyes had both had acute congestive attacks treated by intensive miotics and neither showed synechiæ. It is of course difficult to assess the severity of the congestive attacks in these patients; but in all of the cases they had evidently been of sufficient severity to warrant the regular use of miotics which had dispelled the pain, misty vision or haloes which characterized the attack. The very low incidence of synechiæ among them, including the two instances in which intensive miotics were necessary to control the attack, is therefore, I feel, striking confirmation of the views of Salzmann and Troncoso.

It seems reasonable, therefore, to recognize, as many ophthalmic surgeons in the United States, on the Continent and in this country do, a so-called narrow-angle type of glaucoma in which the form of the angle is itself an important factor in determining the onset of a congestive attack, and encourages the formation of adhesions between iris and cornea. The degree to which these adhesions become permanent and form a serious hindrance to the aqueous outflow has been suggested by Sugar (1941*b*) to depend on the duration of the attack; and the tendency of the eye to develop a subsequent chronic increase in tension upon their extent. According to this view, therefore, although adhesions of the iris root to the trabecula cannot be admitted as the primary cause of congestive glaucoma, their presence over a considerable extent of the angle prevents a return to normal conditions.

Barkan (1938) stated that glaucoma appears to be due, in the majority of cases, to mechanical obstruction of the intra-ocular fluid at some point in its course. He contrasted with the narrow-angle type of the disease (in which he believed the obstruction to be caused by iris adhesions) that type with a deep chamber, where blockage occurred from closure of trabecular pores, either by the deposition on the trabecular surface of pigment, or by sclerosis of the trabecula itself. This latter was to be recognized gonioscopically by a porcelain-like appearance of the trabecula. This conception of a mechanical cause of simple glaucoma has, naturally, focused attention upon the appearance of the trabecula in this form of the disease, the result of which has been a sharp division of opinion. Confirmation for Barkan's view appeared principally from Goldmann's Clinic in Berne (Bangerter and Goldmann, 1941) where evidence of trabecular abnormality as "felting" or pigmentation has been recognized with certainty in some 55% of cases and similar, but less conclusive appearances in a further 30%. Other observers (Sugar, 1940; Busacca, 1945; François, 1948; and others) have been unable to find characteristic trabecular changes in simple glaucoma. However, the fact that most have been able to see the canal of Schlemm fill with blood during gonioscopy in a large proportion of normal eyes, but in only a very small proportion of those with simple glaucoma, has appeared to strengthen the case for a mechanical block at the angle. Trantas (1928), for example, found this absence to be so constant that by observation of blood he

excluded the condition, and François, who finds no other gonioscopic sign pathognomonic, considers that the permanent and constant absence of blood from the canal in chronic simple glaucoma is the sole certain fact to be elicited from gonioscopic examination.

In routine examination of the patients attending the Glaucoma Clinic at the Institute of Ophthalmology it has not been possible to identify a difference in surface appearance which appeared with any constancy among the cases in which the trabecula could be seen. Considerable differences of pigmentation have been noted, some cases showing little or none (and among them are several whose duration is known to be considerable) and others, including some in which the diagnosis has only recently been made, showing dense pigmentation amounting at times to a discrete line of pigment limited to the region of Schlemm's canal.

Blood was noted to appear in the region of Schlemm's canal, during gonioscopy, in 4 of the early cases examined and, in view of the pronounced differences noted in the fit of the gonioprism, pressure upon the post-limbal veins—greater in eyes in which the fit was scleral than in those in which the contact was primarily corneal—seemed likely to be a factor responsible for the appearance or non-appearance of the phenomenon. It was felt, therefore, that the use of a gonioprism in which the fit could be said to be more constantly scleral might result in a greater proportion of cases showing blood filling of the canal. A simple modification of the gonioprism was therefore made by Hamblin who added to the scleral surface of its posterior lip a narrow rim of perspex.

In the 26 glaucomatous patients subsequently examined with this modified gonioprism blood filling of Schlemm's canal could be seen more frequently. Pigmentation of the trabecula was encountered in varying degree, and in some cases obscured the colour change associated with the entry of blood. Thus in 3 instances definite appearance of blood was seen in non-pigmented sectors only; in 4 there was a change of hue suggestive of blood and in 5 others, more densely pigmented, no such change was seen.

TABLE II.—BLOOD REFLUX INTO SCHLEMM'S CANAL IN SIMPLE GLAUCOMA (26 CASES)

Blood filling the canal	Blood in sectors only	Appearances suggestive of blood	Blood not seen
8	8	5	5

In chronic simple glaucoma, I should like to emphasize 3 points:

First: The failure to confirm Barkan's or Goldmann's observations of a trabecular surface appearance characteristic of glaucoma.

The difficulties of recognizing at the trabecular surface, under the magnification possible in gonioscopic examination, an appearance characteristic of an insidious condition such as sclerosis must clearly be great. Nevertheless, since these cases in which it was sought included a number in which the condition was of long standing, it was to be expected that a proportion of them at least would have shown a distinct variation from the normal and from early glaucoma cases. The failure to observe such an appearance would seem to provide reasonable evidence against its existence as an important factor in chronic simple glaucoma, and confirms the findings of Sugar, Busacca, François and others.

Second: Pigmentation of the trabecula does not appear to be a necessary concomitant of glaucoma, since it was absent in several advanced cases, and marked in some with only early signs.

Third: Under suitable conditions, blood can be seen to enter the canal of Schlemm in a sufficiently high proportion of cases of chronic simple glaucoma to cast doubt upon the value of the evidence which its absence has been thought to provide of obstruction at this point. One may usefully add, I feel, that in so far as transparency of the trabecula is necessary to the observation of blood in the canal, its appearance in these cases excludes the opacification which would reasonably be expected to accompany sclerosis of the trabecula. There is, therefore, confirmation for Busacca's observation (1945) that, in chronic simple glaucoma, the trabecula preserves its normal transparency.

Post-operative Gonioscopy.—The surgical measures employed at the angle of the anterior chamber produce, in most cases, alterations in the gonioscopic picture which can be readily identified, and, since purely mechanical explanations can frequently be related to the success or failure of operations, gonioscopy has proved of considerable value in the early detection of postoperative complications and in interpreting the mode of action of various types of operation.

Iridectomy has been generally believed to achieve its success by reopening the irido-corneal angle which has been closed by the apposition of iris to cornea. Troncoso (1925, 1933, 1935), however, found that the extent of the reopening of the angle bore little or no relation to the clinical success of the operation. Tension, he found, may remain normal in the presence of

persistent, total peripheral anterior synechia, including a persistent iris stump in the coloboma, and this when no external evidence of filtration is to be seen. This view has since been confirmed by other observers, notably Sugar (1940) who suggested, however, that small openings in the iris might exist and be responsible for adequate drainage even though they were not gonioscopically visible.

I have, from the notes of the Institute, summarized the findings in 6 cases of acute congestive glaucoma in whom an iridectomy was necessary to control the tension.

TABLE III

Case	Percentage peripheral anterior synechia	Vision	Fields	Clinical result	Time since operation
0069 ..	100	6/12	Constricted to 2/2000 w.	Good	18 months
0070 ..	10	6/18	?	Moderate	20 months
0072 ..	90	6/18	Constricted to 5/2000 w.	Moderate	20 months
0081 ..	70	6/6	Full	Excellent	6 years
0097 ..	100	P.L. Cataract Nebula	—	Poor	7 years
0119 ..	95	6/9	Nasal loss	Good	6 months

In this small group no correspondence exists between the degree of closure of the angle by peripheral anterior synechia and the clinical result; and, if it were presumed that the ill-effects of closure of the angle in this way become apparent only after some time, Case 0081 provides good evidence to the contrary.

These examples clearly support Troncoso's contention that the synechiæ are the result rather than the cause of the hypertension, and suggest that when this cause, whatever it may be, has ceased to act, spontaneously or as the result of surgical or medical treatment, the eye may regain its normal function irrespective of the presence of the synechiæ seen gonioscopically. In this connexion it is of interest to recall the Doyne Memorial Lecture in which Goldmann (1949) described his surprise in observing a normally stratified aqueous vein in an eye recovered from an acute congestive attack and in which the angle was obliterated by total synechiæ, suggesting that, although the angle was apparently closed, aqueous humour continued to pass into Schlemm's canal and find its way to the aqueous veins.

Permeability of the iris forming the synechiæ may well be the explanation, as Sugar suggested, and a rather unusual case which I have examined recently may throw a little more light upon the problem.

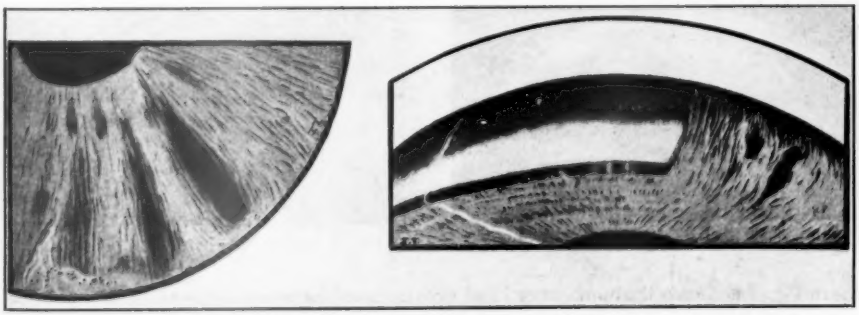


FIG. 3.—A, Iris atrophy (direct view). B, Bridge synechia (seen by gonioscopy).

The illustration (Fig. 3) was made from the eye of a young woman in whom glaucoma was first diagnosed at the age of 7. She is clinically a case of juvenile glaucoma and her only eye shows a deeply cupped disc, very restricted field and visual acuity of 6/18 now, at the age of 37. The iris of the eye is very atrophic with clefts of the anterior layer and stroma of which a good example is shown in the painting (A) of the direct view, where the iris surface will be seen to resemble closely that seen in iridoschisis. With the gonioscope the angle is seen (B) to be deep and widely open in its nasal half; but, on the temporal side, it is obscured by

wide corneal synechiæ continuous with the iris surface and appearing as though there had been a peripheral retraction of the anterior layer. The gonioscopic picture here shows the edge of the synechia which is evidently, under stereoscopic vision, bridging, but not blocking, the angle. This type of finding may well assist in explaining how continued drainage is possible in the presence of an angle obscured by synechia. In this instance free trabeculæ may well remain under the adhesions and, even if the angle were completely obscured in this way, it seems not unreasonable to suppose an iris as atrophic as this to be fairly permeable to aqueous.

After *trephine* operations the condition of the angle as a whole, and not simply the operation site, may be largely altered—a fact which may be of importance if secondary surgery has later to be undertaken. Angles which had been completely open before trephining were first found to be closed after operation by Werner in 1932 and McLean and Sugar (1940) have made similar observations. This closure is generally attributed to the formation of synechiæ during the immediate post-operative period when the anterior chamber is collapsed and for this reason the practice of refilling the anterior chamber with air before the patient leaves the table is practised by some surgeons. Obvious and well-recognized causes of the operation failing to provide drainage are readily seen with the gonioscope in many of the cases in which they occur as obstruction of the trephine hole by iris, ciliary processes or lens. Although retroplacement of the trephine hole often makes examination of it impossible, since the accompanying angle is frequently shallow, its position among the ciliary processes can be verified in some cases.

The gonioscopy findings after 36 trephine operations, chosen at random, but obviously selected, if only from their mode of reference to the Institute, serve to illustrate the frequency of these occurrences. Closure of the angle by 50%–100% synechiæ was seen in 24 cases, by 20%–50% in 2 cases, 5%–20% in 6, and in 4 only were no synechiæ observed. The trephine was seen to be patent in 16 cases, with an adherent stump in 4 of them. In 13 it was blocked or largely blocked by prolapsed iris (5), ciliary processes (6) or lens capsule (2). Two trephines were seen, retroplaced, among the ciliary processes and 5 were not visible.

Whilst adhesions of the pillars of the coloboma or root of the iris do not, in some of the cases seen, appear to obstruct the trephine to any great degree it is perhaps significant that in partial obstruction of the trephine by iris or ciliary processes the tissue involved has the appearance of being drawn rather than pushed up into the trephine-hole, leaving, for example, the free ciliary processes in their normal position, an appearance as though the aqueous current draining through this exit tended to sweep the tissue farther into the trephine-hole.

Fig. 4 illustrates this appearance fairly accurately and shows as well the obscuring of the angle on one side of the trephine by synechiæ, whilst on the other it is clearly open and Schlemm's canal is seen to have filled with blood during the examination.



FIG. 4.—Trephine: prolapsed iris root.



FIG. 5.—Trephine: herniation of lens capsule.

In Fig. 5 is shown the appearance in an eye trephined some ten and a half years ago. The lens capsule has the appearance of being drawn up into the trephine-hole, and I have myself seen an increase in opacification of it and the lens periphery between two examinations at an interval of a month or so. The interval since operation is so long here that it must surely exclude direct operative damage to the lens; and it is tempting to suppose that the condition began with herniation of ciliary processes, followed by suspensory ligament and has now had this effect on the lens capsule.

Fig. 6 shows the appearance of the angle at the operation site in a patient in whom a first trephine controlled tension for a period of four years, after which time a second trephine became necessary. The earlier trephine hole is almost entirely obscured by adherent iris, and the second partly so by ciliary processes, although the patient is clinically stabilized.

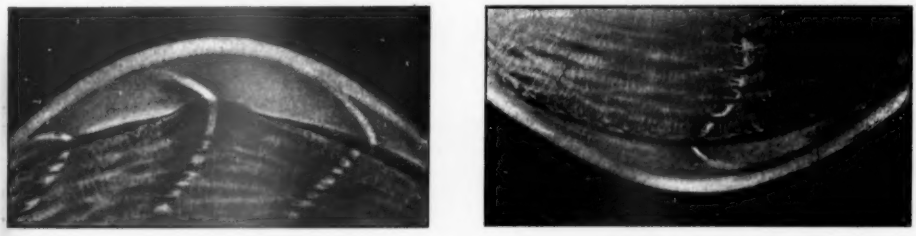


FIG. 6.—Blockage of trephines by iris and ciliary processes.

Heine's (1905) contention when he introduced *cyclodialysis* was that the operation succeeded in controlling tension by providing a new channel between the anterior chamber and the supra-choroidal space rather than by producing a localized ciliary atrophy from the vascular damage of the operation, as was suggested later, notably by Krauss (1908) and Salus (1920). Heine's original view, corroborated by histology, has been further confirmed by gonioscopy. Numerous observers, Vannus (1935), Barkan (1936) and Sugar (1940), to name three, have observed with the gonioscope that there exists after cyclodialysis a cleft between the ciliary body and the posterior annular line in the region of the intervention and the patency of this determines the success of the operation, since, according to Sugar, in unsuccessful cases it is found to be blocked, usually by organized blood clot. I have been able to examine only one eye on which cyclodialysis had been successfully performed and in this I was able to see the cleft.

In *iridencleisis* operations, as Troncoso (1947) points out, the nature of the operation makes the observation of the inner opening of the scleral wound difficult and the fact that the iris is drawn forward and upward to it in the cases I have examined has caused the iris to obscure much of the upper part of the angle. Sugar (1942), however, has reported an appearance of visible separation of the lips of the wound in 79% of successful cases and finds that, in a large proportion of them, most of the gap is entirely free of uveal tissue. The fact that the anterior chamber reforms rapidly after the operation is probably associated with a reduced tendency for peripheral anterior synechiæ to form, according to Troncoso and, certainly in three eyes which I have examined after this operation the maximum percentage of synechia was estimated to be five.

In the few cases of *Preziosi's operation* I have examined, the region of the cautery puncture has been clearly visible, usually with iris adherent to it, either at the posterior lip or appearing as a tubular adhesion around the circumference. Synechiæ are remarkably few, as is shown



Region of puncture in upper field. Angle in lower field.

FIG. 7.—Preziosi cautery puncture.

in Fig. 7 in which the pigmented trabecula is visible throughout the fields, and I understand that in this operation also, reformation of the anterior chamber usually occurs early.

The utility of gonioscopic examinations will doubtless increase. Its value as far as treatment is concerned is a personal one showing clearly the results of one's own interventions against the background of one's experience of the individual operation, rather than in a general review such as this, made in ignorance of the actual operative details. It may help, as Sugar (1941*a*) and Kronfeld and McGarry (1944) have contended, to assess the danger of a congestive attack by demonstrating the degree of embarrassment of the angle by synechia or moderate mydriasis with drugs; and, as American writers have suggested, pre-operative knowledge of the site of synechiae may, by enabling them to be avoided in subsequent surgery, render this easier and freer from hæmorrhage.

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Mr. Arthur Lister said that he had had some experience of goniotomy for hydrophthalmia, an account of which might be of some interest.

He had asked Mr. Tarrant, the artist, to draw the picture (Fig. 1) from a description of the typical appearance so that the picture was actually only drawn from hearsay. It was, however, a fairly good representation of the angle in a typical case of hydrophthalmia. The white band at the root of the iris covering the usual details of the trabecular zone and the ciliary band, had been present in all the hydrophthalmic angles he had examined in babies. In a patient of 27 who had achieved a spontaneous cure the angle was particularly interesting. In the left eye the angle was closed by a white substance and there was no sign of the ciliary body at all, but in the right eye (which had 6/18 vision) the angle was quite well open although the ciliary body appeared to be covered by a sort of thin veil. It looked as if spontaneous cure was achieved by the stretching of the material until it became permeable and allowed the aqueous to drain normally.

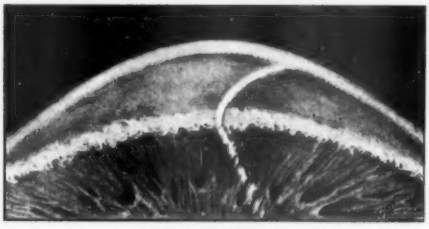


FIG. 1.

It was this band of embryonic tissue which was considered to be the cause of most cases of hydrophthalmia by, among others, Barkan and Ringland Anderson, and it was this band which the operation of goniotomy was designed to divide. The details of the operation were fully described by Barkan in the *British Journal of Ophthalmology*, 1948, **32**, 701, but it was interesting to record that operations with a similar aim, although they might not have been based upon such an accurate knowledge of the pathological anatomy of this condition, were employed by de Wecker in 1869 and de Vincentiis in 1893.

His own experience of goniotomy ran to 9 cases, to which might be added 4 which Mr. Harold Ridley kindly allowed him to quote. He followed Barkan's technique as far as possible, but he found that a modified Saunders' needle, ground down so that the blade was thinner than the shaft, was easier to use than Barkan's knife. He also found Barkan's operating contact lens so big as to fill up the whole conjunctival sac. He therefore got Hamblin to make a much smaller contact lens which was very easy to manage: it did not give much magnification but with it and a binocular loupe one could see sufficiently into the angle to put one's knife there. Actually he had only used it once for operation but quite often for looking at the angle. The number of cases in which one could use a contact lens was not very large.

His own 9 cases supported Barkan's observation that goniotomy was only likely to succeed in early cases where the cornea was not greatly enlarged or altered, and that it was no use trying it when the cornea was larger than 14 mm. Out of the total of 13 cases (23 eyes), 6 (9 eyes) or 46% might be considered to be definitely successful so far; 2 cases were definite failures, the remainder being either partially successful or doubtfully attributable to goniotomy. In the successful cases sometimes two or three goniotomies were necessary, sometimes only one; in all his own successful cases the history was six weeks or less and in 4 the corneal diameter was not more than 13·5 mm.

There were two important and obvious criticisms to be made; the first was that almost any operation had a good chance of success in the early and mild cases. None, however, was so cosmetically perfect or injured the eye so slightly; there was a risk of hæmorrhage but if one was careful and did not try to do too much of the angle at a time this risk was slight.

The other criticism was the length of follow-up. His cases had all been followed up for about two years now and they had all been all right so far, but the most critical period he thought would come round about puberty. One found so many cases in which, although a spontaneous arrest or an apparent operative cure was effective for the first nine or ten years, during the teens drainage ceased, tension went up and vision deteriorated. Then, therefore, would be the time when goniotomy would be tested.

Dr. M. Klein said that he would like to draw attention to the difference between high magnification and low-power magnification gonioscopy, in which a Troncoso gonio-lens, a headloupe and a good focal light are used. With this method patients could be examined in the outpatient department as it took only a few minutes. The cases in which he had found it useful were such as those described by Mr. Hobbs, for example foreign bodies in the angle of the anterior chamber. In a case of iris sarcoma which he saw at Mr. Wolff's clinic with this gonioscope one could see how far back it went, and this helped to arrive at the decision that the tumour could be removed by iridectomy. Low magnification gonioscopy was not suitable for research purposes but it was a great help clinically in suitable cases and should be included in the routine equipment of the ophthalmologist.

Hereditary Bilateral Ptosis and Blepharophimosis Associated with other Developmental Abnormalities of the Outer Eye.—M. KLEIN, M.D.

In a 3-year-old boy ptosis, epicanthus, blepharophimosis, dystopia of the lower lacrimal puncta and hypoplasia of the caruncles were noted. The levators and superior recti were also involved.

Vision of the right eye 6/12, of the left eye 6/6. There is no appreciable refractive error. Ocular movements show limitation of upward movement but there is no vertical deviation. Fusion is good with an amplitude of approximately from −2 degrees to +20 degrees.

The lids cover the upper third of the pupil. Levator action is absent, and though the upper lid is soft one can feel that the levator-tarsal layer is fibrotic. In the father, who has the same condition, this thickening and fibrotic change in the upper lid is even more marked. The ptosis is associated with blepharophimosis, and in such a case it has been suggested that the shape of the palpebral fissure is responsible for the ptosis, and operation should aim at enlargement of the palpebral fissure.

The dystopia of the lower lacrimal puncta, the hypoplasia of the caruncles, the epicanthus, and the wide opening of the two inner canthi correspond, according to Waardenburg (1930, 1932), to conditions found at the fœtal age of 8 to 10 weeks, and he assumes that this stage of development becomes fixed. The absence of levator action and involvement of both

superior recti are probably due to absence, or developmental abnormality, of these muscles (Fig. 1).

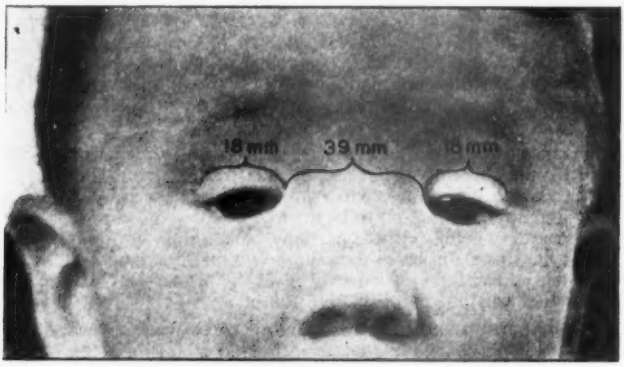


FIG. 1.

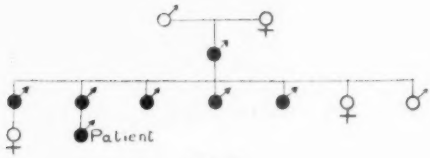


FIG. 2.

The pedigree shows that the condition first appeared in the grandfather of the patient, and no previous member of the family was affected. He transmitted it to five sons. A daughter and a sixth son were free (Fig. 2).

Similar family trees have been published and this one resembles that of Dimitry (1921). Usher (1925) published a pedigree where ptosis was linked with epicanthus, and in some members both conditions were present, in others only the epicanthus.

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Mr. Frederick Ridley said that an important point had been omitted. This was an Icelandic family, and the condition was new in Iceland. It looked as if the grandfather was a genetic oddity who developed this condition *de novo*.

Mr. Maurice Whiting said that he would not touch the levator muscle in this case since it appeared to be defective and it would not be much use to shorten a defective muscle.

It would be better to do an external canthotomy, not too much—as this would exaggerate the distance between the inner canthi—and then to put in two narrow fascia lata grafts so as to get a slight raising of the lid. One could not make the eyes look normal, but it would improve the appearance and uncover the pupil to the normal extent.

Mr. B. W. Rycroft said that a number of these cases were seen from time to time at East Grinstead and the practice was to carry out a canthoplasty. This was done by the plastic surgeon. Afterwards a Blaskovicz resection was done. Movement was not obtained by either method but a Blaskovicz operation gave the better cosmetic result.

Section of Urology

President—Professor CHARLES WELLS

[*May* 25, 1950]

THE following Cases and Specimens were shown:

(1) **Massive Solitary Local Recurrence of Hypernephroma.** (2) **An Unusual Vesico-Colic Fistula.**—Professor CHARLES WELLS.

(1) **Adenoma of Kidney.** (2) **Swab Forming the Nucleus of a Bladder Stone.**—Mr. JAMES CARVER.

Renal Tumour (Parenchymal Carcinoma).—Mr. D. P. KENNEDY (introduced by Mr. H. K. VERNON).

(1) **Multiple Carcinomata of the Ureter.** (2) **Carcinoma of the Renal Pelvis.**—Mr. RICHARD A. MOGG.

Bilateral Staghorn Calculi (Further report on case previously discussed).—Mr. H. J. MCCURRICH.

(1) **Stone from Ureterocele.** (2) **Lateral Uretero-Vesical Anastomosis.**—Mr. ALEX. E. ROCHE.

(1) **Bilateral Ureteric Calculi; Transvesical Lithotomy.** (2) **Left Ureteric Calculus (in Ureterocele); Transurethral Removal.**—Mr. R. D. WILKINS for Mr. WILFRID ADAMS.

(1) **Conglomerate Stone in a Diverticulum Simulating Multiple Vesical Calculi.** (2) **Diverticulum Associated with Solitary Vesical Calculus and Benign Hypertrophy of Prostate.**—Mr. H. N. G. HUDSON.

True Hermaphroditism.—Mr. J. D. FERGUSSON.

Tumour of Epididymis.—Mr. F. J. MILWARD.

Elephantiasis of Scrotum.—Mr. C. G. SCORER.

[*June* 22, 1950]

DISCUSSION ON PARTIAL NEPHRECTOMY

Mr. Howard G. Hanley: *A Collected Review* (*Abridged*).—The Council of this Section thought it unlikely that any one urologist would have enough personal cases to produce a really authoritative report on the subject of partial nephrectomy, and it was suggested that I should try and collect at least a hundred cases from other surgeons. I should like to thank all of my many colleagues who have made this collected review possible. The opinions expressed are largely my own, but I will attempt to indicate the contrary view of others where necessary.

A brief review of the literature shows that the first deliberate nephrectomy operation was carried out by Gustav Simon in 1869, and eighteen years later, in 1887, a deliberate partial resection of a kidney was performed by Czerny. Partial nephrectomy is therefore no new operation.

During the following early days of renal surgery up to 1900, many authors, including Tillman (1879), Tuffier (1891), and others, showed that partial resection was quite a feasible procedure in the treatment of localized renal pathology. However the operation rapidly lost favour, probably due to its being employed in unsuitable cases such as in tuberculous and malignant lesions. The early writers lay great emphasis on the risks of hæmorrhage during and after operation, and also on the development of persistent urinary fistulæ, while serious infection must always have been a hazard.

In the early nineteen-hundreds, a more conservative approach to renal surgery returned, and such lesions as cysts, benign tumours, localized cortical abscesses, localized hydro- or

pyo-nephroses and localized disease in a double kidney, were all subjected to partial resection by various surgeons anxious to avoid a complete nephrectomy. Even so, the total number of partial resections recorded in the world literature up to 1937 was under 300 (Goldstein and Abeshouse), and only a very few of these were British.

In reviewing the literature and in discussion with various colleagues, it becomes obvious that there is some confusion over the nomenclature, the terms Heminephrectomy, Partial Nephrectomy, and Partial Resection, all being used indiscriminately, and I consider that we should use the term heminephrectomy for the removal of half—even an unequal half—of a double kidney, reserving the term partial nephrectomy for all the various resection operations other than those for double kidney and the resections of pelvis for hydronephrosis. By this simple classification, all cases where renal tissue is removed can be placed in two main groups:

Heminephrectomy referring to removal of the half of a double kidney, be it unilateral, crossed ectopic, or horseshoe, and *Partial Nephrectomy* including removal of portions of parenchyma for localized disease, calycectomy and resection of cysts.

The subject of *Heminephrectomy* is not very controversial; all urologists agree that the correct thing to do where a half of a double kidney is diseased is to remove that half. Personally I have very little experience of such cases. I have removed a half of a horseshoe kidney on one occasion. This was twelve years ago and I would now have divided the isthmus and attempted a plastic operation for the hydronephrosis. I have *seen* 43 double kidneys, but have only had to perform heminephrectomy in three instances—once for an ectopic ureteric opening, once for stone, and once for renal pain.

However this is a relatively commonly performed operation in this country and my colleagues have provided me with data about many such cases.

A patient of Mr. R. H. O. B. Robinson's is a typical example. He had complained of pain in the left loin and dysuria for six years. A plain X-ray showed a calculus in the upper renal pole, but the excretion pyelogram (Fig. 1) demonstrated that it lay in the upper half of a double kidney which was subsequently resected. The patient was alive and well eighteen months later (Fig. 2).

Heminephrectomy is a certain cure for the incontinence due to an ectopic ureter; but in such a case of my own, there was a very well-developed, uninfected half-kidney, and I have often wondered whether I should not have transplanted the ureter to the bladder rather than perform the heminephrectomy.

Mr. H. K. Vernon (1945) showed a very interesting example of this condition to the Section of Urology, and there have been many others.

[There were some excellent photographs and heminephrectomy specimens on the table which came from Mr. T. L. Chapman of Glasgow, Mr. R. K. Debenham of Birmingham, and Mr. David Band of Edinburgh.]

The technique of heminephrectomy for a double kidney appears to be straightforward. Most surgeons make a point of tying off the vessels of the kidney to be removed and report that in a majority of cases there is a reasonable line of cleavage. Hæmostasis appears to be obtained by mattress sutures generally reinforced by muscle or fat. I will refer to this subject later on.

Indications for Operation in Heminephrectomy.

Table I shows the indications for operation in some 48 cases of heminephrectomy collected from twenty urologists. The list is incomplete since I did not specially ask for data about heminephrectomy cases and many surgeons have deliberately excluded such patients from their series. There is a high incidence of ectopic ureteric openings.

TABLE I.—HEMINEPHRECTOMY

Hydronephrosis and/or hydro-ureter ..	13
Ectopic ureteric opening	13
Calculi	9
Small infected pelvis	5
Infected half of horseshoe kidney ..	4
Pain	4
Total	48

Cases from:

Messrs. Badenoch, A. W., Band, D., Carver, J. H., Chapman, T. L., Davis, J. Llewellyn, Debenham, R. K., Donovan, H., Hanley, H. G., Higgins, T. T., Jacobs, A. H., Lane, T. J., Millin, T. J., Mogg, R. A., Moore, T., Pyrah, L. N., Riches, E. W., Robinson, R. H. O. B., Stewart, H. Hamilton, Vernon, H. K., Winsbury-White, H. P.

A most interesting group is that marked PAIN. These cases come from Mr. R. K. Debenham and Mr. Arthur Jacobs, and all four were young women in the early thirties. The only symptom was pain localized to the small poorly developed upper pelvis, and they were completely relieved by heminephrectomy. I have two such women who visit me annually. I could always reproduce their pain by distending the pelvis; and stimulated by the reports of these four cases, I have since performed a heminephrectomy on one of them, but it is too early to say whether the relief of pain will be permanent.



FIG. 1 (*Case* 1).—Excretion pyelogram showing stone in upper half of a double kidney.



FIG. 2 (*Case* 1).—Excretion pyelogram after heminephrectomy.

We now come to the true *Partial nephrectomy group*, much more controversial and much more interesting.

For the sake of completeness I will refer briefly to solitary cysts. *Some* of these shell out perfectly easily and there is no trouble with bleeding, but this is not always so. I have operated upon five large renal cysts but only managed to get three away without a total nephrectomy. The other two had such extensive perirenal adhesions that the line of separation between cyst and kidney could not be defined. Other urologists report similar findings. Both radiologically and clinically at operation, it may be impossible to differentiate between a large closed-off hydrocalyx, and a solitary cyst. A simple solitary cyst may dissect out nicely, but an infected one or a hydrocalyx certainly will not, so that a true partial nephrectomy through healthy parenchyma will be necessary.

Indications for Partial Nephrectomy.

Partial nephrectomy would appear to be the operation of choice where the pathology is confined sharply to one area of the kidney, and where the blood supply remaining is adequate to support the tissue left behind. Also the tissue remaining should probably be capable of performing at least half of the function of the affected kidney. Such recorded lesions as hydatid cysts, benign tumours, persistent urinary fistulæ, and localized infections including carbuncles and infarcts have not been encountered in this review.

The 155 partial nephrectomy operations under consideration are shown on Table II. 125 were performed for calculus disease, including 12 bilateral cases. There were 9 operations for hydrocalycosis and 9 for solitary cysts. This cyst group is incomplete since I did not specially seek information about such cases. 8 partial nephrectomies were performed for tuberculosis and will be discussed in detail later on with the neoplasm group. The 2 hydronephrosis cases underwent a lower pole resection because a large aberrant vessel required

ligaturing. Undoubtedly, the chief indication for the operation is a stone lodged in a dilated, generally lower, calyx. If the stone is fragmented, appears to be irregular in outline, of low radiological density and fits the calyx snugly, I think that the chance of removing it completely is so remote that nothing short of a partial resection of the whole calyx offers any real hope of avoiding a recurrence.

TABLE II.—PARTIAL NEPHRECTOMY

155 *Operations*

For Stone		
Resection of upper calyx	.. ..	41
Resection of lower calyx	.. ..	83
Resection of middle calyx	.. ..	1
Bilateral resections	.. .. ..	12
	Total	125
For hydrocalicosis	.. ..	9
For solitary cysts	.. ..	9
For tuberculosis	.. ..	8
For neoplasm	.. ..	2
For hydronephrosis	.. ..	2
	Total	155

Cases from:

Messrs. Anderson, J. C., Badenoch, A. W., Carver, J. H., Chapman, T. L., Debenham, R. K., Donovan, H., Freshman, E., Hanley, H. G., Jacobs, A. H., Kilpatrick, F. R., Lane, T. J., Millin, T. J., Moore, T., Parker, G., Pennell, V. C., Pyrah, L. N., Rees, H., Riches, E. W., Roche, A. E., Semple, J. E., Stewart, H. H., Winsbury-White, H. P.

I first saw the patient depicted in Fig. 3 with a very severe pyelitis of pregnancy in 1946. There was a " plug stone " in the left pelvis and multiple calculi in the lowest calyx. Her infection was controlled with pelvic lavage and she was carried to full term.



FIG. 3 (*Case* 2).—Pyelitis of pregnancy with a "plug stone" in the pelvi-ureteric junction and calculi in a dilated lower calyx.



FIG. 4 (*Case* 2).—Post-natal excretion pyelogram.



FIG. 5 (*Case* 2).—Retrograde pyelogram three years after operation.

Fig. 4 shows a post-natal excretion pyelogram. The debris in the lower calyx is well seen; the hope of removing all of this mud by a pyelo- or nephro-lithotomy would be remote. A partial resection of the whole lower pole was performed together with a pyelolithotomy, and Fig. 5 is a retrograde pyelogram taken two months ago—three years after her operation.

One of the largest series of partial nephrectomy cases for stone belongs to Mr. T. J. Lane of Dublin, and he has shown microscopically that even if the removal of the stone or gravel is complete, the calyx is deformed and its lining membrane is eroded or even destroyed, being replaced by granulation tissue, while the parenchyma undergoes the changes characteristic of chronic interstitial inflammation. Fig. 6 is an X-ray photograph sent to me by



FIG. 6 (from Mr. T. J. Lane).—X-ray photograph of resected lower pole showing areas of diffuse calcification.

Mr. Lane showing a resected pole with areas of calcification. The risks of stone recurrence in such calyces need no emphasis.

I do not know where stones *commence* to grow, but they certainly tend to fall into the lowest calyx, so that if this calyx is very dependent and shows any irregularity, its resection does remove the " sump", with the result that any subsequent stones are not caught there, but are rather encouraged to pass down the ureter whilst they are still small. In the case of stones in an upper calyx with a narrow neck, the removal of the whole calyx is still advisable since, as Lane has shown, the lining mucosa is generally replaced by unhealthy granulation tissue.

A localized hydronephrosis or hydrocalycosis caused either by a stone or a stricture of the neck of the calyx is another lesion suitably treated by local resection. These hydrocalycoses, even if free from stones, may give a persistent pyuria and can cause chronic renal pain. The contraction of the calycine neck is said to be due to a chronic pyelonephritis. Hyams and Kenyon (1941) refer to the condition as "localized obliterating pyelonephritis" for which they advocated partial nephrectomy.

Fig. 7 shows a good example of such a lesion which was the cause of a persistent pyuria



FIG. 7 (*Case* 4).—Infected upper pole hydrocalicosis in a single kidney. Infection completely relieved by resection of upper pole and hydrocalicosis.

and loin pain. It was the only kidney the patient possessed, but I resected the upper calyx and she has remained free from pain and infection for over three years.

The preservation of as much renal tissue as possible is absolutely essential in many cases. There are numerous examples in the literature of disease processes in solitary kidneys, of serious bilateral renal injuries and, much more commonly, of bilateral pathology such as calculus disease. In this present review there are many instances of removal of one kidney and a partial removal of the other. In Lane's series alone there are 10 bilateral partial nephrectomies and 10 lithotomies on one side and a partial resection on the other. Most fortunately these lesions generally occur in the upper or lower calyx thus admirably lending themselves to wedge resection. I have several times encountered a stone in a damaged middle calyx and have always thought that a resection here would be impossible, but this is not so, for Mr. E. W. Riches has removed a middle calyx on more than one occasion.

In this series I have collected 125 cases of *partial nephrectomy for calculi*, 41 in the upper calyx, 83 in the lower calyx, and 10 mixed. 13 operations were for recurrent stones and in 12 instances the resections were bilateral.

Fig. 8 from a bilateral calculus patient is interesting. The large right pelvic stone was removed first of all, and a Davis intubation of the pelvic-ureteric junction was performed.



FIG. 8 (*Case* 7).—Plain renal X-ray.

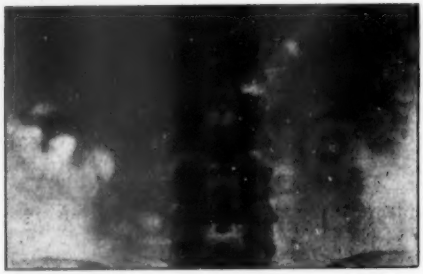


FIG. 9 (*Case* 7).—Two years after a right pyelolithotomy with a "Davis" intubation of the obstructed pelvi-ureteric junction, and a left heminephrectomy.

Later, the lower pole of the left kidney was resected with its two soft stones, and the pelvic stone was removed through the open lower calyx.

The excretion pyelogram Fig. 9 was taken recently, two years after operation.

The *calculus recurrence rate* after this operation is impossible to estimate since many of the patients have not been followed up for a long enough period. However, there are 14 known recurrences. Mr. Lane has observed his resections for stone over a ten-year period and I should like to quote his remarks: "Recurrences occurred in 11 cases. Of these recurrences the stones or gravel were got rid of without surgical interference in 3 cases; in one instance a nephrotomy was done; in one a superior calicectomy and in one a ureterolithotomy was done; slitting the ureter transurethrally in one case enabled the stone to be got rid of; a re-resection of the inferior pelvis was done in one case; in 3 cases nothing further was done."

Mr. Riches had one recurrence in 13 partial nephrectomies, and he subsequently performed a nephrectomy on this patient.

Of my own 19 cases, 2 recurred; both patients had bilateral calculi and the recurrences developed within six months. In one case the kidney had already been operated upon previously and at the time of the partial nephrectomy I was unsuccessful in relieving the serious degree of pelvi-ureteric obstruction so that a stone recurred within three months. In view of the fact that a ureteric stone had recently been passed from the other kidney, I performed a secondary nephrolithotomy. However, a fistula developed due to the ureteric obstruction and a nephrectomy was necessary. Incidentally the remaining kidney has since developed a further stone.

My other recurrence also developed within a few months and the stone which was removed at a secondary pyelolithotomy turned out to be practically hollow—I presume it had formed round a blood clot. Fig. 10 shows some sandy mush at the bottom of the right lower calyx, and three months after removal of this calyx there was a very satisfactory pyelogram, Fig. 11. However, the retrograde film, Fig. 12, was taken three months later still and shows a recurrent hollow stone in the pelvi-ureteric junction.

We thus have a recurrence rate of 14 in 125 operations, or 11·2%, but this figure may be on the low side as I mentioned previously. However, a study of the recurrences shows that they were practically all in seriously complicated cases with bilateral or already recurrent disease. A nephrectomy would certainly have prevented recurrence, but was not always practicable, or in the patient's interest.



FIG. 10 (*Case* 8).—Sandy debris in lowest right calyx.



FIG. 11 (*Case* 8).—Three months after right partial nephrectomy.



FIG. 12 (*Case* 8).—Six months after operation showing recurrence of a hollow calculus in the pelvi-ureteric junction.

Tumours and Tuberculosis

We now turn to the more rare forms of pathology which have been treated by local excision. These include *Tumours and Tuberculosis*. The bad results which originally followed partial nephrectomy for these lesions were responsible for the abandonment of the operation in earlier days.

However, with the more careful selection of cases, there may well be a very definite indication for the operation today. If a simple tumour can be diagnosed with certainty before or at operation, it can be safely removed by partial nephrectomy; the literature records examples of successful resection of malignant tumours from solitary kidneys, or where the other kidney was thought incapable of supporting life alone (Rosenstein, 1932). Goldstein and Abeshouse (1937) collected 21 resections in the literature performed for malignant tumours with only one operative death, and 13 resections for simple tumours without any mortality. They also record 6 partial nephrectomies for adherent pararenal or adrenal growths without any complications. In selected cases where one kidney is damaged and an early growth is detected in the other, conservative resection probably has a place, being perhaps better than allowing the patient to die from his primary lesion. This may all sound rather theoretical but Mr. T. J. Millin has a case in which he removed one kidney for a hypernephroma, to be followed six months later by a partial nephrectomy for another growth, possibly a new primary. This patient was alive and well four months after the second operation. Mr. A. W. Badenoch also has a patient in good health some years after a partial nephrectomy for what was thought at the time to be a solitary cyst, but which on section proved to be a hypernephroma. Cases of this sort will be rarely encountered, but it is important to remember that the immediate prognosis may not always be hopeless.

Referring now to *Tuberculosis*, one finds that the subject of local excision keeps cropping up as more and more cases are recorded. In 1937 Goldstein found 41 examples in the literature. There were 5 deaths, 5 post-operative fistulæ and 6 secondary nephrectomies. Even so with the advent of the newer antibiotics the treatment of early renal lesions may have to be modified. In recent years I have observed several tuberculous lesions confined to one calyx for many months on end. The patients were well, they had no other tuberculous focus and yet after a long period of quiescence the lesion seemed to extend suddenly, rendering a nephrectomy necessary. Even then one or two of these kidneys have had a very localized area of destruction which might well have been resected.

Everyone agrees that the new antibiotics are no substitute for surgery, but they may well render our surgery less drastic. A combination of chemotherapy, sanatorium regime and conservative surgery should be the ideal therapy, and even if sanatorium regime is not available in this country, I think nephrectomy is an admission of defeat. There is now ample evidence that certain tuberculous lesions can be resected from a kidney with complete and lasting success, and as in all branches of surgery, improved results will follow, not only improved operative techniques, but more careful management and selection of cases.

A very important paper on conservative surgery in renal tuberculosis came from Carl Semb of Oslo last year (1949). Being an eminent thoracic surgeon he naturally considers the surgery of renal tuberculosis on the same basis as that of pulmonary tuberculosis, and divides his cases into three groups:

Type A: Infiltration without macroscopic destruction; the so-called "parenchymatous" form of renal tubercle. He believes that this form will heal spontaneously or with the help of medical treatment.

Type B: With local destruction, or cavity formation—the "ulcerocavernous" form of renal tubercle. He points out that the spontaneous healing of such a demonstrable cavity in the kidney is even less common than in the lung. Local surgical resection is the procedure of choice in such cases.

In Type C, with total destruction, nephro-ureterectomy is still the correct treatment.

Semb records 14 patients upon whom he performed partial nephrectomy. A bilateral resection was carried out in 2 cases and both were alive and well after a year, one with a tubercle-free urine. In all, 5 of his patients had bilateral disease. It is also of interest that not only did he resect the middle portion of the kidney on three occasions but in one case he removed both upper and lower poles, and the post-operative pyelogram still shows an excretion shadow. Two patients at the end of this treatment were each left with one-half of one kidney and are in good general health. These operations were performed with no mortality, and with no urinary fistula, post-operative bleeding or spread of disease. Most of the cases are too recent for a critical assessment, but 4 of the 5 patients treated a year before were free from tubercle bacilli, the fifth one having undergone a bilateral resection. Semb believes that streptomycin, particularly post-operatively, is invaluable.

The operative technique of partial nephrectomy for tubercle must differ somewhat from that used for stone. In the latter cases, a calycectomy is probably all that is necessary, but for tubercle a much more radical resection is needed.

Let us now consider our present collection of cases. Fig. 13 shows an X-ray of a young woman with a shadow in a lower calyx. Her only complaint was of long-standing right-

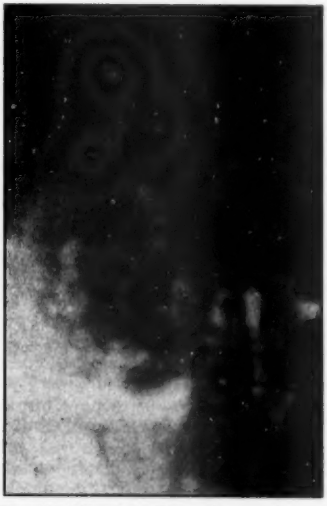


FIG. 13 (*Case* 9).—Excretion pyelogram.



FIG. 14 (*Case* 9).—Excretion pyelogram four years after resection of right lower pole.

sided pain. The routine examination of the urine showed pus cells and some mixed organisms and this lower calyx was resected without any complications. To my discomfiture the so-called calculi turned out to be areas of calcification in a tuberculous lesion. That was four years ago, and although living tubercle bacilli were isolated from the resected calyx, the patient is alive and well today, with no tubercle bacilli in the urine (Fig. 14).

Mr. Hamilton Stewart has a case of successful partial nephrectomy for tubercle, while Mr. Geoffrey Parker performed a left nephro-ureterectomy for tuberculosis followed by a right heminephro-ureterectomy for a similar lesion in a double kidney. The X-ray [exhibited at the meeting] shows the lower half of this right double kidney two years after the heminephrectomy.

Mr. T. J. Millin has 5 patients from whom he successfully removed a tuberculous lesion, one of these being bilateral, so it is obvious that we cannot disregard such conservative surgery as purely experimental, and I, for one, think that there may be a real future for partial nephrectomy in renal tuberculosis.

The Literature and Experimental Work

In 1880 the first true nephrotomy was performed by the English surgeon Henry Morris (1885). He removed a stone from an infected kidney and using no sutures at all, merely inserted a drain into the kidney and packed all round it. This was completely successful and stimulated surgeons all over the world to follow his example, and to modify the procedure in their own way. Tuffier (1891) was the first person to use catgut sutures passed through the kidney substance to close his incision, but in a very short time Israel (1901), Albarran (1909), and others all introduced modifications and practically every method and pattern of suture and material was used. Packing with catgut threads, fascia lata, muscle, fat, &c., were all tried.

Papin (1928) quotes Tschalka Hilse and Armin as having first used fat for hæmostasis in 1913. Since then much experimental and clinical work has been done on this subject. Koll of Chicago (1917) reported success with fat grafts and then Lowsley (1933) and his co-workers introduced their method of closing the renal capsule with ribbon gut having first of all filled up the nephrotomy wound with a fat plug. Lowsley's principle of closure with or without the use of ribbon gut is the method I have used in most of my cases and I have found it eminently satisfactory. The great majority of authors condemn the use of any form of deep mattress sutures to approximate the cut surfaces and control hæmorrhage. Herbst and Polkey (1930) showed a serious degree of necrosis following mattress sutures in all of their animal experiments. Personally I find it quite unnecessary to place any sutures in the parenchyma at all provided there is a good capsule, but, of course, the capsule is a very variable structure.

In recent years several surgeons have advocated the use of the diathermy cutting current for the kidney incision, since they assert that there is less bleeding at the time of operation. Personally I am not worried about bleeding at the time of operation but feel that the inevitable necrosis round a diathermy incision is much more likely to lead to a delayed hæmorrhage later on.

The experimental work on the subject, though scanty, does support this view. Yunck and Forsyth (1941) resected the calyces of 10 dogs with a scalpel, and of 3 dogs with the diathermy. The only deaths in the series occurred in these 3 dogs. 2 died on the fourth and fifth days; both had urinary extravasation and the site of the incision showed marked local necrosis and absence of healing with the suture line open. The third dog was sacrificed at the end of a week and showed necrosis and an abscess at the operation site. This supports my own findings—I have only used the diathermy twice and on one of these occasions serious bleeding continued for ten days and a secondary nephrectomy was performed. Statistically, of course, all this means little, since other surgeons use the diathermy with success, but I personally shall continue to use the scalpel.

The next subject is that of *compensatory hypertrophy* following wedge resection. Much experimental work has been done here also and it appears that the removal of small portions of one kidney (up to one-third) is not accompanied by hypertrophy if the other kidney is intact (Valentin, 1893; Rosenstein, 1932). Some workers (Herbst and Polkey, 1930) even think there is some relative atrophy of the resected kidney, as shown by reduction in average size, weight and function.

If more than half of the total renal tissue is removed, i.e. a nephrectomy followed later by resection of a third to a half of the other kidney, a compensatory hypertrophy occurs in all cases. Resection of one-half or less of a solitary kidney is always followed by compensatory hypertrophy, and this is a very comforting thought.

Both experimental and clinical studies indicate that human beings can live normally with only a quarter of their total renal tissue. I have 2 patients living in perfect health four and six years respectively after an extensive partial resection of a solitary kidney. These patients certainly only have a third of their original total renal tissue.

Operative Technique

I should like to stress that the following account is a description of the method I use, but I will try to indicate from time to time any important differences which have been encountered during this review.

A good surgical exposure is essential and for this and all other renal operations I go through the bed of the twelfth rib. The kidney requires adequate mobilization and the vascular pedicle must be fully exposed. In the majority of cases I rely for hæmostasis on the assistant gripping the pedicle between his index and middle fingers. This has the advantage that the kidney then lies in the palm of his hand and is held firmly during the resection. However, the interossei soon tire, and the bleeding may not be as well controlled as one could wish f the resection takes longer than usual.

The use of a very light curved clamp protected by rubber tubing will give complete hæmostasis, but may not always be easy to apply if the pedicle is short. Furthermore there is still the problem of holding the kidney in position for resection. Incidentally it has been asserted that one can leave a clamp on the renal vessels for a considerable time without doing irreparable damage, but I find this hard to believe (Van Slyke *et al.*, 1944).

Some of my colleagues use tapes round the pedicle—I have not tried this but it sounds very reasonable.

It is almost essential to have a good pyelogram which shows the renal outline as well as the calyces, since the amount of parenchyma between the surface and the calyx varies from case to case, and without this information it is difficult to decide just how much tissue to remove in order to bring the wedge up to the neck of the calyx.

The first gross difference in technique I encountered was the shape of the wedge to be removed. I have always made the incision so that there are medial and lateral flaps, but Mr. V. C. Pennell and others always use anterior and posterior flaps. Mr. Pennell also attempts a meticulous closure of the calyx in the apex of the wound so as to avoid fistula formation.

However, having decided upon the area to be removed, the capsule is incised and reflected back as far as the proposed lines of incision and the wedge removed with a scalpel (Fig. 15).



FIG. 15.—Excised wedge: showing artery forceps on reflected capsule.

The spurters, if any, arise from the vessels in the centre of the parenchyma round the calyx. I think it is a waste of time trying to catch these in artery forceps and tie them. As soon as the plug of fat is placed in the gap and the capsule is brought over to hold it in place, the bleeding stops. There is no need to have any great tension on the capsule sutures but they should be fairly close together to prevent the fat herniating through the gaps (Fig. 16). It should be noted that in this method of closure, no attempt is made to approximate the opposed surfaces of the wedge-shaped gap under tension. I originally used ribbon gut as

recommended by Lowsley until I realized that there is no need to have any tension on the capsule unless the latter is very thin, in which case ribbon is very useful. Even when the capsule *is* very thin there is rarely any need to use deep mattress sutures. I never cease to marvel how the bleeding stops immediately the fat plug is in situ. Why fat is so effective for this purpose I do not know. I think it just plugs up the holes mechanically—but it certainly is effective.



FIG. 16.—Capsule loosely sewn over fat plug. Further sutures necessary to prevent fat herniating through the gaps.

Some surgeons use mattress sutures to approximate the lips of the incision in direct apposition, and, for what it is worth, I have already referred to the experimental work on mattress sutures. Frequently, mention is made of reinforcing the suture line with an overlay of fat or muscle to aid hæmostasis. Now this I cannot understand. The serious bleeding comes from the apex of the wedge round the neck of the calyx—not from the cortex. The fat should be in the wedge—not outside it. I agree that the fat outside the capsule may stop the sutures cutting through, but there again there is no need to tie them as tight as this. The same applies to oxycel unless it is applied inside the gap.

Several surgeons seek for and tie off any vessels going to the pole to be resected. If the operation is merely a calycectomy, I try and avoid doing that because I have confidence in the fat plug, and feel that the tissue left behind will require all the blood supply it can get. Where the whole renal pole is being removed the problem is probably different. In tuberculous cases Semb stresses the fact that an avascular field is very necessary when large openings into the pelvis and major calyces are being carefully resutured. He therefore uses a light pedicle clamp and also ligatures the segmental vessels in the hilar region. He closes the parenchymal wound by inserting fibrin foam between the cut surfaces. The capsule is then closed to prevent loss of blood and urine. So far I have never done a nephrostomy or a pyelostomy in association with a resection and on only two occasions have I drained the kidney bed. Over this latter point I am in a minority, but I am unrepentant. As a rule the urine is blood-stained for several days and there may even be clot colic, but I consider that there is less risk of infection occurring if there is no drainage to the surface.

Post-operative Complications and Morbidity

It is always difficult to assess the morbidity of any operative procedure when reviewing the literature, or when collecting cases from various surgeons, no matter how detailed the case histories may be. The chief complications listed in the literature are secondary hæmorrhage and persistent urinary fistula, both perhaps necessitating secondary nephrectomy.

Hæmorrhage is the commonest complication referred to by urologists contributing to this review, and the fear of post-operative bleeding is, I believe, the chief factor which prevents

the operation from being employed more extensively, for there are obviously many definite indications for its use.

There is no doubt that in some cases there is more loss of blood than occurs during a nephrectomy, and this bleeding may continue for several days, but, even so, it is nothing to the loss which may occur following prostatectomy.

Clot retention in the bladder occurred in 12 instances. The bleeding in 7 cases was severe enough to require transfusion, while 5 patients were said to have had "troublesome hæmorrhage".

There were 2 secondary nephrectomies for continued bleeding but when we remember that the alternative to partial nephrectomy in a majority of these cases would have been a total nephrectomy, the net saving in good functioning kidneys is very considerable.

The next complication is *Urinary Fistula*, but I think the risk of this has been greatly exaggerated. Personally I have had no case of fistula so far. In fact there are only nine fistulæ in the whole series. 2 of these were serious, lasting several months, and followed heminephrectomies, but the other 7 all followed partial nephrectomies and closed spontaneously within five days. Interestingly enough the majority of fistulæ developed where the wound was drained, and I believe the less we drain, the fewer fistulæ we shall get. Even so fistula formation is obviously not a serious hazard of this operation.

Mortality is a much more positive feature than morbidity, much less likely to escape entry in the case notes. When we consider that total nephrectomy has a not inconsiderable mortality, the value of partial nephrectomy becomes ever more obvious. In 1935 I reviewed 200 cases of total nephrectomy for all causes in two teaching hospitals and one special urological hospital and found that the operative mortality was 10·7% (Special Hospital 4·8%; General Hospitals 13·9%). The ultimate mortality after five years, in 182 patients, had risen to 28%, and most of these deaths were due to some condition related to the urinary tract, chiefly to failure of the remaining kidney (Hanley, 1940). It is therefore obvious that until we can estimate renal function far more accurately, we should consider the possibility of a partial nephrectomy on every occasion before performing a total nephrectomy.

Goldstein and Abeshouse (1937) found that partial nephrectomy caused a mortality of 5·4% of the 296 cases in the literature up to 1937, so that British Urologists may be justly proud of the fact that the 203 hemi- or partial-nephrectomy operations in this series were performed with only one operative death.

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Mr. E. W. Riches said that his own list of 19 cases of partial nephrectomy comprised 2 of double kidney with complications, 4 of calyceal diverticulum (hydrocalicosis), 1 being upper and 3 middle, and 13 cases of stone in a dilated calyx, 1 in the upper, 1 in the middle, and 11 in the lower.

Of the first group he showed one picture—a case of double kidney, with the ureter from the upper half of the right kidney draining into the urethra. The patient had undergone two operations for stress incontinence before the true cause was found; heminephrectomy cured the incontinence. The next case he showed was one of calyceal diverticulum with the cavity filled with stones. He had expected to see examples of this condition in Mr. Hanley's series, but he had not shown them. He had had 6 such cases, and he did not think the term "hydrocalicosis" was applicable; it was really an encysted collection of calculi and he thought the name calyceal diverticulum was preferable. He now did partial nephrectomy for the

condition, but in this particular woman he took out the stones and obliterated the cavity with sutures and a muscle graft. Sixteen months later the patient came back with a similar collection in exactly the same place. There was again a cavity filled with stones, and this time he carried out a nephrectomy. It seemed to him that there was a great tendency for the pelvis or the calyces to maintain cavitation unless the whole stone-bearing area of mucous membrane was removed. In doing partial nephrectomies it was necessary to be sure to remove all the mucosa as there was a tendency for the outlying part of the calyx to reform after operation.

He showed another example of a cavity in the middle of the renal cortex filled with stones. This was treated by a wedge resection from the convex border of the kidney. He did not remove the calyx at all in this instance, but he removed the cavity containing the stones. The pyelogram six and a half years later was normal and showed no stones. He had another example in the upper pole, with a more obvious communication with the calyx.

Though complications were rare he would like to discuss them a little further. In the case of which he showed illustrations he amputated the upper pole. The wound healed and the urine became sterile. Two months later the patient came back with an abscess which opened, and she had a urinary fistula. Lipiodol was injected into the fistula and a pyelogram taken, which he showed. It took about two months for the fistula to heal, and this was the longest period he had known, four months after operation. Another intravenous pyelogram taken one year and nine months after operation was normal and showed no stone; the urine was sterile. It was encouraging to know that fistulæ of that sort would heal and he thought the injection of lipiodol was a great help.

Mr. Riches mentioned briefly the third group, those with stones in a dilated calyx. These were mostly in the lower calyces and relatively easy to remove, but he showed one also in the upper calyx. The pyelogram showed an irregular cavitation and a collection of stones in the upper part of the right kidney. There it was necessary to excise the upper pole. Three months later the X-rays showed that there was still one small stone in the kidney, but fortunately the patient passed this. An intravenous pyelogram six months later was normal. Of all stones the best type was the pear-drop stone in the lower calyx. He showed a case operated upon in 1939; the pyelogram seven years later showed the kidney to be normal.

In removing part of the kidney he thought it important to remove an adequate amount. He liked to make his wedge either anteroposterior or from side to side as appeared best in each case.

To summarize he felt that this was a very satisfactory operation and that the results were permanent. Mr. Hanley had spoken about the technique, and he differed from him only in minor ways. He thought it most important to keep the capsule. Sometimes it was friable and if it was over an inflamed lower pole it might be adherent, but it must be kept at all costs and replaced afterwards. He generally used diathermic cutting current for the section. He used a muscle graft in place of the fat favoured by Mr. Hanley, taking the muscle from the abdominal wall and crushing it with Spencer Wells forceps. He generally put in one or two mattress sutures and tried to bring the sides of the wedge together. On one occasion he used hæmostatic gauze in place of muscle graft, but he did not think it had any advantage.

The question of suturing cut mucosa separately would always arise. Theoretically it was better to close up the neck of the calyx with a fine suture, but it might not be easy and he was not always very particular about it.

There had been relatively few complications. Mr. Hanley had said that his correspondents had not informed him of any, but he at least had done so. He had one recurrent stone, a bilateral case, and had to do a nephrectomy on one side. There was a recurrent *B. coli* infection in a woman who had a normal post-operative intravenous pyelogram; the infection was controlled with streptomycin, but it always recurred.

He was interested in the successful cases of partial nephrectomy for tubercle, but was not very convinced of the wisdom of the procedure; he looked upon tubercle as a generalized infection, and he did not feel that if they were just excising a local focus they were really going to cure the patient. It might have its use in selected cases.

Mr. Arthur Jacobs said that because so much of their time was spent in removing organs and structures, it was a real joy to carry out conservative procedures on the kidney whenever the opportunity presented itself. That was why he was glad they were having this discussion and he felt that Mr. Hanley was to be congratulated on a splendid opening paper. He himself had carried out 18 partial nephrectomies and in 13 of these the operation was for stone. One of his more recent cases was so typical of the variety which lent itself to partial nephrectomy and in which that operation was the one of choice that he would show the illustrations of it. He then exhibited pyelograms to demonstrate the long-term results of partial nephrectomy for stone.

The recent case referred to was a woman just over 40 who had had a stone removed from the lower pole two and a half years ago. Another stone had formed and occupied a cavity in the upper pole, an end projecting into a calyx. The retrograde pyelogram taken three weeks after operation showed the result obtained. Apart from the absence of the upper calyx the pyelographic appearances were normal. The pyelograms next shown to demonstrate long-term results were:

(*a*) Right retrograde pyelogram, female aged 68; lower pole resected five years previously.

(*b*) Intravenous pyelogram, male aged 51; lower pole right kidney resected three years ago and left kidney removed a year later for multiple recurrent calculi.

(*c*) Right retrograde pyelogram, female aged 31; resection of lower pole containing 2 calculi, two and a half years ago. Operation preceded by combined pyelo-nephro-lithotomy for 3 stones in left kidney.

(*d*) Left retrograde pyelogram, male aged 52; lower pole resected eighteen months ago.

With regard to operative technique, he had almost invariably used mattress sutures consisting of double strands of very fine chromic catgut. He had observed no disadvantage from their employment and the pyelograms he had shown demonstrated a very satisfactory renal status.

Mr. H. Hamilton Stewart brought forward 71 cases in which partial nephrectomy had been done during the nine years 1938–47. In 61 of these cases the operation was performed for calculi. Of the other cases, in 3 the operation was performed for double kidney, lower part infected, in 3 for double kidney upper ureter draining into vagina, in 3 for cysts, and in 1 for tuberculosis. He felt that the kidney tissue which secreted urine into the calyx containing a calculus was probably pathological. If a stone were seen in the pelvis or ureter then he asked himself whether there was any radiological evidence to indicate in which calyx this stone had matured. A careful examination of the X-ray films often enabled one to discover certain abnormalities, such as calycectasis affecting an isolated calyx or a further stone in a calyx or fine debris adherent to the fornix of the calyx, or fine calcification in the cortex of the kidney in close relationship to a calyx. In these cases, after removal of the calculus from the pelvis or the ureter, he carried out a polar resection either at the same time or subsequently. He showed slides illustrating this condition and the results of operation. He drew attention to a stone in the ureter which evidently originally was impacted in the neck of the top major calyx causing dilatation of the minor calyces. The stone was removed and an upper polar nephrectomy performed. In another case of stone, if the intravenous pyelogram were examined a dilatation of the calyx would be observed. In this case the stone was removed from the ureter and an upper polar partial nephrectomy performed. In another case of stone the intravenous pyelogram showed a dilatation of the top minor calyx. In that way one was able to discover the site of origin of the calculus in the ureter. In this case the stone was removed from the ureter and then at the subsequent operation the upper pole of the kidney was also removed. Another example showed a stone in the pelvis of the kidney, and on examination of the upper and lower pole a fine calcification was observable. At operation, therefore, he removed the stone and at the same time carried out an upper and lower polar partial nephrectomy.

Of his 61 partial nephrectomies for renal calculi in the period 1938–47, the lower pole was resected in 79%, the upper pole in 16·4%, and both poles in 3%, and in 1·6% the upper pole was resected and calculus removed from the middle calyx. In 9 cases stone was removed from the renal pelvis or ureter. As for the composition of the stones, this was phosphate in 33%, oxalate in 48%, and both minerals in 19%. The report of the pathological sections showed calcareous deposits in kidney tissues in 29%, and pathological changes in the kidney (including calcareous deposits) in 88%. He felt, however, that if more thorough investigation were made, the figure for calcareous deposits would be much higher than 29%.

He had endeavoured in the available time to follow up these 61 cases, but only 30 had so far presented themselves for follow-up X-ray examination. He hoped in due time to examine the others. In these 30 a recurrent calculus was seen in the region of the middle calyx in one case; the other cases were free. The recurrence was in a case of upper polar partial nephrectomy.

It was not possible from these figures to make any definite deductions, but it appeared that the recurrence of calculus formation was less likely after resection of an affected pole than if the calculus alone were removed. The risk of operation was no greater than that of an ordinary nephrolithotomy. There appeared to be a 79% chance that a stone seen in the pelvis or ureter had matured in a lower minor calyx. He felt that if a case were seen in which a calculus was present in the pelvis or ureter it was one's duty to attempt to discover the calyx in which the stone had matured. This portion of the kidney should, in his opinion, be removed.

Mr. H. P. Winsbury-White said that he had never done a partial nephrectomy for a tuberculous case. He had always felt in such cases that one was never sure whether one was clear of the whole of the lesion. He had carried out partial nephrectomy only in 10 cases, but he had practised it in three types of case, and it had always involved an amputation of the lower pole of the kidney. He had done it in 7 cases for calculus. In 2 cases he had done it in hydronephrosis where a blood vessel at the lower pole had to be divided because it was obstructing the ureter. He had deemed it proper to take away the lower pole because of the danger of necrosis. Finally, in one case he had carried out the operation where there was hydronephrosis with double pelvis.

With regard to the type of operation, he just cut the kidney across and having always secured the vessel to the lower pole, passed a number of through-and-through sutures through the parenchyma, half an inch apart and half an inch from the cut margin. He had divided the renal tissue with a knife and had never had any embarrassment from bleeding, especially after having secured the vessel in question. He had done a certain number with wedge resection, using anteroposterior flaps and diathermy. He thought the bleeding was slightly less with the diathermy needle, and that was his method of choice at present.

He thought it very important to do a wedge resection. In the earlier cases he did not do that, and he found that a considerable time had to elapse before the urinary fistula healed. In one case it went on for a couple of months. It shortened the convalescence to do a wedge resection.

With regard to mortality in this modest series, he lost one of his cases—a case of bilateral renal calculus in a man of 39 with rather badly damaged kidneys, with a stone in the upper end of each ureter. He removed the stone from the right ureter and resected the pole of the right kidney which contained stones. The patient, however, was obviously on the edge of a precipice, and in this case the blood urea which was within normal limits gave one a sense of false security.

He had not experienced secondary hæmorrhage in any of these cases. He always made a point of putting a corrugated rubber drain down the suture line of the kidney and left it there until the risk of urinary leakage was passed. Concerning flaps, he had never tried fat or muscle such as other speakers had mentioned. He had found the simple through-and-through suture passed with a round-bodied curved needle to be quite satisfactory. He had never bothered to close specially the mucous membrane of the main calyx.

Professor V. W. Dix said that he always used mattress sutures and had not had any trouble with them. Of 6 operations on solitary renal cysts performed in the last year, 3 had been true partial nephrectomies. They had all healed without any trouble. There had been no urinary fistula, and no post-operative temperature. Nevertheless, in 2 of these cases pyelograms in the third week after operation showed dye outside the kidney, and he was now waiting to perform pyelograms in these cases after an interval of several months, in order to see whether the kidney had healed.

He also asked whether it was really necessary, when one divided a lower pole vessel and saw the change in colour of the kidney, to resect the lower pole. In his experience the infarction had had no unfortunate after-effect.

Finally, he suggested that it might not be necessary to carry out heminephrectomy in every case of ectopic ureter. He had implanted three of these ureters into the bladder in 2 patients with good results.

Mr. A. W. Badenoch showed some illustrations which would amplify some of the indication for partial removal. In renal duplex when disease was localized to one-half of a double kidney they should attempt to remove this half always providing it was a safe procedure. He showed illustrations of a case with a hydronephrosis in the lower half and a normal upper half, when the operation was easily done. The second case showed stone formation in the lower half with the upper half normal. In this case at operation it was quite impossible to find a line of cleavage and he had to do a complete nephrectomy. In regard to partial nephrectomy in renal tuberculosis, one of his own cases was a man aged 22, with renal duplex and tubercle bacilli in the urine. The slide showed dilatation of the upper half of the right kidney and the lower half, while a little dilated, looked comparatively normal. At operation there were a few tubercles on the outer surface of the kidney near the upper pole. In this case a complete nephrectomy was done. The specimen showed a small lesion in the upper half with tubercles on the upper ureter, the lower part of the kidney and the lower ureter were normal, but the common ureter was studded with tubercles. He felt convinced that in this case had only half the kidney been removed, the disease would not have been cleared up on that side. He was rather doubtful as to whether they should engage in chipping off small

portions of kidney in tuberculous disease, when without really splitting the kidney they could not say how extensive the process was.

His next illustration was of bilateral calculi—one in the pelvis of the kidney and a collection in a calyx in the left kidney. The latter side was treated by partial nephrectomy.

He showed a case of neoplasm in which he had done a partial nephrectomy, in a woman aged 58. At operation there was a large smooth cystic swelling about 16 cm. in diameter. Influenced by the fact that the renal artery conveniently divided into two, one supplying the kidney and the other the cyst, he did a heminephrectomy. The swelling was a hypernephroma necrosing at the centre.

He showed a retrograde pyelogram taken six months after the nephrectomy. She was free from symptoms and there was no evidence of metastasis when seen nearly eighteen months after the operation.

Mr. J. A. Pocock showed slides of 2 cases of hydronephrosis in a double kidney and described a third which had been seen during the last few months. One case presented with painless hæmaturia and the other as an acute *Bacillus coli* infection of the kidney. Such cases were suitable for heminephrectomy, but whether or not this could be carried out depended on the blood supply to the remaining pole of the kidney.

Heminephrectomy in tuberculosis would appear to be an unorthodox form of treatment, as he had always regarded it as a generalized disease necessitating removal of the ureter as well as the kidney, the whole operation being carried out without even drainage of the renal bed. He would like to agree with Professor Dix who considered that the risk of dividing a lower polar vessel had been exaggerated.

Mr. Hanley (in reply) said that Mr. Riches and he had discussed the difference between dilated calyces and hydrocalicosis, and frankly he did not yet know the truth of the matter; it called for further observation. He had been greatly impressed by Mr. Hamilton Stewart's cases, most of which were not included in his series. In reply to Professor Dix, he agreed that there was no need to resect the lower pole when one had divided the artery. He had frequently divided the aberrant vessel and not resected, and nothing untoward had happened. Mr. Badenoch had answered most of Mr. Hamilton Stewart's points about stones in the calyces. In reply to Mr. Pocock, he had drained only 2 of these cases.

Section of Surgery

President—DIGBY CHAMBERLAIN, Ch.M., F.R.C.S.

[*April* 5, 1950]

DISCUSSION ON THE TREATMENT OF CHRONIC ŒDEMA OF THE LEG

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Chronic lymphœdema still continues to resist surgical cure. In fact one may state categorically that the condition, ever since Lisfranc in the first half of the nineteenth century treated it by scarification of the limb, has proved one of the most disabling and disheartening to the patient and one of the most disappointing in its treatment to the surgeon.

Chronic lymphœdema falls broadly into two groups:

(*a*) Parasitic, due to blockage of lymph channels by the adult forms of *Filaria bancrofti* or *Filaria malayi*.

(*b*) Non-parasitic, due to lymphatic obstruction from other causes.

The parasitic form occurs only in tropical climates and its distribution coincides with that of filariasis. It will not be further considered here. The non-parasitic form may be met with anywhere in the world and is common throughout the British Isles. It occurs in four distinct forms:

(1) *Congenital and familial lymphœdema* (*Milroy's disease*, 1892, 1928).—This rare disease is probably due to a congenital lymphangiectasia. Many reported cases are not true examples of the condition.

(2) *Idiopathic lymphœdema or lymphœdema præcox*.—This is commonly encountered in Great Britain in adolescent females. It has an insidious onset and a painless progress. It can produce enormous enlargement of one or both legs. Though it is said to be non-inflammatory it is probable that the lymphatic damage is due to a low-grade inflammatory process for in the later stages many cases exhibit typical attacks of inflammation.

(3) *Elephantiasis streptogenes nostras or inflammatory lymphœdema*.—This follows repeated erysipelatous attacks often spreading from nodal points in the legs. With each attack swelling becomes more pronounced, the causative organism being either a streptococcus or a staphylococcus. The clinical course of the disease is characteristic and unmistakable.

(4) *Secondary lymphœdema* comprises a mixed group in which the cause is usually clear. Venous insufficiency and other vascular disorders predominate.

From this large group of cases idiopathic and inflammatory lymphœdema accounts for the majority of chronically swollen arms and legs in Great Britain, in which surgical aid is sought.

Surgical Considerations

True lymphatic œdema can be produced by many agencies but in all cases the actual mechanism is the same. Drinker and Field (1933) have shown that obstruction to the main channels of lymphatic escape from the limb produces œdema which can become chronic. Progressive destruction of the large lymphatics, by internal blocking, by intimal sclerosis or by external pressure, is followed by dilatation of the peripheral network of lymphatics. The valves become incompetent, the protein content of the retained fluid is high and progressive fibrosis of the waterlogged limb follows. Attacks of inflammation in the sea of lymph begin to occur even when inflammation has not been clinically evident at the onset of the disease. Thus the vicious circle is complete and the damage to the lymphatic endothelium progressive and irreversible. Eventually there comes a time when, even if the obstruction were completely relieved, the normal *vis a tergo* responsible for the onward flow of lymph would be quite incapable of emptying the dilated network or of overcoming the effects of gravity.

The anatomy of the lymphatic system.—All tissues, except the placenta, possessing blood vessels also have lymphatic vessels—in fact the evidence suggests that the latter form a sort of accessory venous system. The lymph vessels begin in a closed capillary bed without stomata and have no communication with other body spaces. Drinker and his colleagues

(1934) have shown that the vascular endothelium allows salts, electrolytes and proteins to pass through into the tissue spaces from which proteins are differentially absorbed into the lymphatics through the lymphatic endothelium. The subepidermal layer of lymphatic capillaries is rich and freely anastomotic over fairly ill-defined focal areas, but anastomosis between these focal areas is poor or absent. These focal areas are drained by short collecting lymphatics into much longer, valved supra-aponeurotic trunks. These larger draining vessels are few in number, and are so polarized by valves of such strength that retrograde injection is impossible without rupture of the walls. They end in regional lymph nodes without again anastomosing with each other. The subaponeurotic deep lymphatics begin and end in the same way and little if any anastomosis takes place between the two systems. The most important barrier to the establishment of any such anastomosis is obviously the presence of fascial planes. As a result of the peculiar disposition and construction of the lymphatic system it is clear that peripheral obstruction can be fleeting in its effects while central obstruction is the almost universal requirement for the production of chronic œdema. Experimentally it is exceedingly difficult to produce chronic œdema as the oft-quoted experiment of Reichert (1926, 1930) so clearly showed, but Drinker and Field have been able to demonstrate that the extent and duration of the lymphœdema depend on the nature, extent, situation and duration of the obstruction and lastly upon the ability of the individual to develop a compensatory lymph circulation or to regenerate vessels to replace those destroyed.

The objects of surgical treatment are clear when we bear in mind the pathology of the condition.

(1) The retained lymphatic fluid may be drained into other channels peripherally thus reversing the lymph flow. This idea first stimulated Sampson Handley in 1908 to attempt drainage of œdema fluid into the normal tissues of the chest wall and abdomen by means of silk threads. Walther (1919) used rubber tubes and Lanz (1911) fascial strips inserted through the deep fascia into the bone marrow. Kondoleon (1912*a*, *b*) devised the operation which sought to create an anastomosis between the superficial and deep lymphatics. This operation modified by Sistrunk (1918, 1927) and Ghormley and Overton (1935) has been widely practised. It would be freely admitted by almost everyone with experience of it that very few patients derive lasting benefit and that not more than 25% of patients are improved by more than 25%. Occasionally mass reduction in size confers some benefit but on the whole it is a very disappointing operation. Practically every patient, however, with chronic lymphœdema has at some time or other been submitted to it.

In defence of it one can say that it is the only straightforward operation yet described which is within the compass of the general surgeon and which offers even a modicum of hope to the patient. Improvement, if there is to be any, can only be attained by very careful post-operative elastic rubber bandaging maintained for at least one year.

(2) The central obstruction may be by-passed: Gillies and Fraser in 1935 proposed the grafting of a lymphatic bearing bridge of skin from arm to leg or from one arm to the other, inserted in such a way that one end lay in the œdematous tissue of the affected limb and the other projected into the nearest available lymph drainage area. In the case of the leg, the lymphatic wick projected into the axilla, with the arm into the opposite axilla. In all cases the polarity of the lymphatics in the graft had to correspond with those in the limb. It may fairly be said that the results were better than with Kondoleon's operation and that the wick actually functioned. But it would not do so in the erect posture when the lymphatic valves in the affected limbs were incompetent and the *vis a tergo* was insufficient to propel the retained fluid upwards. With the arm or leg elevated, however, rapid emptying took place and the patients reported that the lymphatic bridge fairly tingled with the outpouring of fluid. Those cases with ulceration of the skin were definitely benefited. The operation is, however, lengthy and difficult to the point where it should not be performed by other than plastic surgeons with a knowledge of flap transfer.

(3) Total removal of the lymphatic bearing area: This idea is not new. Charles in 1912 described in detail the treatment of a case of filarial elephantiasis in which he excised all the subcutaneous tissue from the leg and covered the limb with free skin grafts. Homans (1936) and Mowlem (1948) reported success with this method. Recently in New York I saw several cases dealt with by Stephenson with encouraging results but the magnitude of the operation made it less impressive. As it seemed that there was little evidence that the existing skin cover of the limb was primarily diseased, I asked Mr. John Watson and Mr. Norman Hughes to undertake a series of cases in which after resecting all subcutaneous tissue and deep fascia down to muscle, they would replace the skin of the limb cut to a thickness approximately that of a Wolfe graft. Such a proceeding would have the advantage of greater economy of skin and less disturbance to the patient than flaying him elsewhere. They have carried this procedure out on 8 patients, 7 in the leg, 1 in the arm; 6 were idiopathic, 1 congenital and 1 filarial in origin. The operation is carried out in two or more stages and

the grafts opposed to the muscles under suitable pressure. The grafts took surprisingly well despite their large size and in only one case was a slough troublesome.

The results in these cases have been impressive and the method deserves further trial. It may be that the grafts act as a kind of strong elastic stocking preventing the accumulation of further fluid. It may be that the removal of practically all the lymph-bearing tissue is curative. It is of course impossible to strip the limb completely, especially round the tendo achillis and the foot, so that one can only say that, where removal has been complete, recurrence of œdema has not taken place. In my view after considerable experience of the three methods which I have described, this is the most hopeful but it is not one which could be commended as suitable for any but a plastic surgeon. Failure with these enormous grafts might have serious consequences.

Conclusion.—The foregoing is a brief description of a plastic approach to a surgical problem which is itself the end-result of a condition which should be medically curable in the earliest stages. I look forward to the time when the inflammatory process originally responsible can be brought under control as surely as with other inflammations and that the all too common condition of chronic lymphœdema will become a rarity.

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WALTHER, C. (1919) *Bull. Acad. Méd. Paris*, **82**, 262.

Professor A. M. Boyd, *Department of Surgery, Manchester:* In selecting the subject of "Swollen Legs" for discussion by this Section, the Committee has wisely chosen a common condition seen in the out-patient departments of all general hospitals and which, because of the vagueness of the underlying causes, has not received sufficient attention. The relief of the physical and mental distress caused by the heavy, unsightly, and often painful limb merits the most intensive study. The necessity for careful and detailed observation of many cases over long periods of time has deterred the most enthusiastic investigators. The invitation to open this discussion provided the necessary stimulus to the Manchester Neurovascular Team to attack the problem in a systematic way. The range of investigations which have been required has been so wide as to put the problem beyond the scope of any single individual. Not only has meticulous clinical study been necessary but biophysical, biochemical and physiological techniques have also had to be invoked. The large number of cases which have to be seen and the amount of data accumulated to obtain a comprehensive picture of the subject demand the attention of a specialist team working in close collaboration in all phases of the problem. Only by this method can any hope of success be entertained.

As representative of the Manchester Neurovascular Team, I propose to give an outline of the general methods of investigation which have been employed.

From an analysis of 673 cases a tentative classification has been adopted. The following types have been recognized:

	No. of patients
(1) Venous	405
(2) Erythrocyanoid	168
(3) Lymphœdematous	69
(4) Angiomatoid	31

In this paper I propose to deal only with the first three groups. Venous œdema may occur at any age and is generally characterized by pain and commonly accompanied by stasis pigmentation; there is a marked tendency to progress eventually to dermatitis and ulceration.

The erythrocyanoid type (Fig. 1, A, B and C), on the other hand, usually becomes apparent in the second decade and is painless, the most marked characteristic being cyanosis of the back and outer side of the leg; pitting œdema is slight, the progressive swelling being due to the deposit of subcutaneous fat leading to marked cuffing at the ankles. This reaches its zenith towards the menopause.

The lymphœdematous type most frequently begins during the second or third decades with a painless pitting œdema involving both legs. The clinical manifestations of the three types are largely dependent on the circulatory state of the limb in which they occur, a factor which complicates the diagnosis. Clinical observation has shown that there are two basic types of limb from a circulatory point of view: the leg in which angiography shows arteries and veins of a "normal" calibre, and the leg with congenitally hypoplastic vessels, the calibre of which is greatly reduced (Fig. 2, A and B). In the first there is an adequate reserve



A B C

FIG. 1.—Erythrocyanoid type. A, early; B, intermediate; C, late (menopausal).

and ability to increase the blood flow when required to overcome inflammatory or other pathological conditions. In the second, which is always on the verge of ischæmia, there is little reserve or ability to meet pathological demands. The erythrocyanoid leg is invariably associated with hypoplastic blood vessels. The venous and lymphœdematous groups are inevitably much modified when occurring in conjunction with an inadequate vascular reserve. A "white leg" occurring in a limb with normal circulation may resolve completely whereas a similar degree of venous obstruction occurring in a limb with hypoplastic blood vessels shows less tendency to do so. Similarly in lymphœdema the progress of the disease is more rapid in the leg with poor circulation. The severity of both conditions, therefore, depends largely on the anatomical and physiological state of the limb in which they occur.

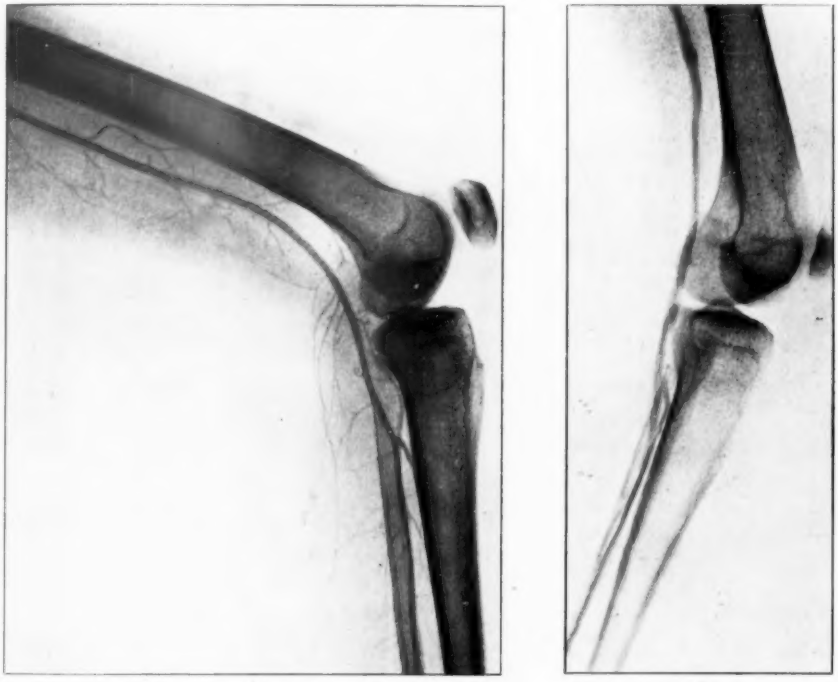
Methods of Investigation

Before commencing investigations the basic factors controlling the interchange of circulatory and tissue fluids were reviewed, and the possible ways in which this process might be modified were discussed. Consideration was given to the extent to which changes might become irreversible as it was known that prolonged bathing of tissues in œdema fluid led to fibrosis. The reversibility of the swelling was studied by noting the rate and degree of subsidence with elevation of the limb, and by mercurial diuresis. Blood volumes were estimated before and after the procedures. Biochemical investigations were made of

the œdema fluid collected by insertion of fine polythene tubing into the subcutaneous tissues. The chronicity of the process was estimated by soft tissue X-rays.

For reference purposes the legs were photographed; antero-posterior and lateral views were taken. The size of the limb was estimated by measurement of the circumference at fixed levels and by volume displacement of water.

The pressure in a superficial vein on the dorsum of the foot was measured by a modification of the method introduced by Mr. A. J. Walker of St. Bartholomew's Hospital. A base line was obtained with the patient standing and was found to be approximately equal to that of a column of water of the height of the right atrium. A standard exercise was performed by the patient "marking time". The results fell into two groups, one where the pressure dropped to 30 cm. of water or less, the other showing little or no change. The absence of



A B

FIG. 2.—Angiograms showing hypoplastic vessels typical of the erythrocyanoid type. A, arteriogram; B, venogram.

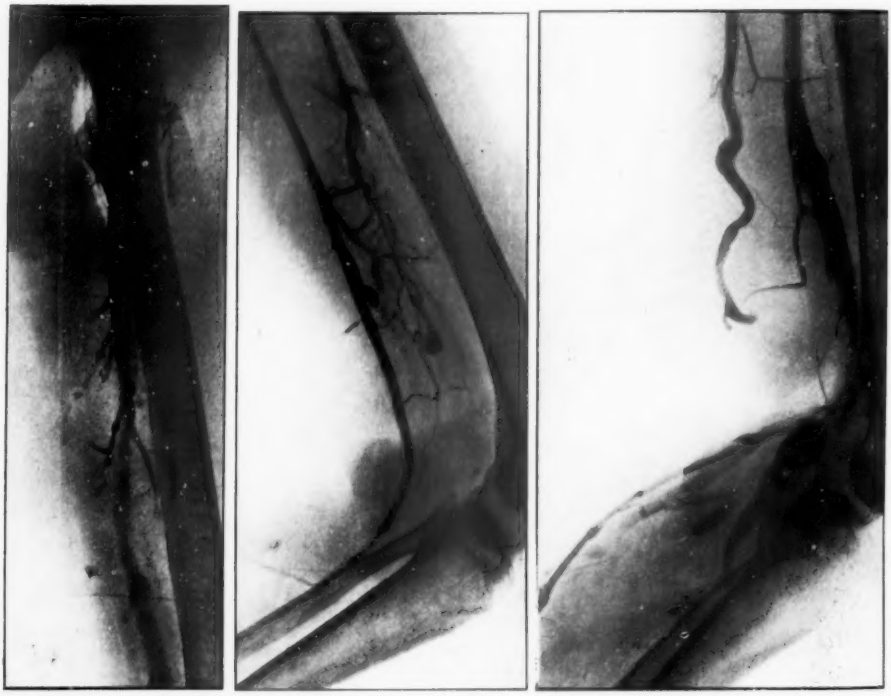
reduction of venous pressure on exercise was found to be a reliable indication of serious delay in venous return.

Walking with the superficial veins occluded by means of an Esmarch bandage was found to be a satisfactory clinical test. Pain occurred in all cases with severe deep venous obstruction.

The extent and site of deep venous obstruction were visualized by a series of angiograms. An ascending phlebogram was obtained in the earlier cases by the direct method—one of the posterior tibial venæ comites being exposed below the medial malleolus and 15 c.c. to 20 c.c. of contrast medium injected. This technique was employed by the Surgical Professorial Unit at St. Bartholomew's Hospital in 1935 (Knight, 1938). The presence of unhealthy tissue below the medial malleolus makes incision undesirable. Indirect phlebography by injecting the contrast medium into a superficial vein on the dorsum of the foot—a pneumatic cuff inflated to a pressure of 50 mm. of mercury being applied above the ankle to ensure the injected fluid passing into the deep circulation—has been employed since 1938. More recently it was found that the cuff was redundant. The competence of a deep femoral valve situated below the entrance of the profunda vein was verified by the injection of 5 c.c. of contrast medium into the common femoral vein. Where the valve was competent no contrast medium entered the superficial femoral vein. If the valve had been

destroyed contrast medium flowed freely down the femoral vein. Similarly a descending injection of the internal saphenous vein proved the competence of the valves in the popliteal vein, the contrast medium entering the superficial femoral vein through the perforating vein in the lower third of the thigh which joins the femoral immediately above the highest valve in the popliteal vein (Fig. 3, A, B and C). If the valve was not competent contrast medium flowed down the popliteal vein into the calf. By these three phlebograms any deficiency of the valves of the deep venous system was immediately revealed. The oscillometer was used for the routine examination of the arterial system. In cases of doubt arteriography was employed.

Advantage was taken of the exposure of the common femoral vein to remove an inguinal gland for biopsy. Sections were also made of the skin, subcutaneous tissue and deep fascia in the œdematous area.



A B C

FIG. 3.—Routine venograms: A, descending femoral venogram showing reflex filling of femoral veins. B, descending saphenogram showing absence of filling of popliteal vein due to thrombosis. C, descending saphenogram showing reflex filling of popliteal vein and upper third of calf veins including the external saphenous.

The results of these investigations together with the case history, gynæcological opinion, and routine clinical observations were recorded on a standard *pro forma*.

(1) *Venous Œdema*

(i) *Ilio-femoral thrombosis.*—Of 405 cases of venous œdema 80 were caused by ilio-femoral thrombosis. The thrombosis most commonly extended from the adductor opening to the level of the hypogastric vein (Fig. 4A). Occasionally, however, the occluded segment ended just below the profunda femoris vein or extended proximally to include the external iliac vein. The causes of the lesion were listed as puerperal, post-operative, traumatic and spontaneous. Puerperal ilio-femoral thrombosis is the cause of the classical "white leg" and needs no further elaboration. The "postoperative" lesion is most commonly seen in those patients over 40 who are confined to bed after operation or for other reasons, particularly pneumonia, typhoid or other febrile conditions.



FIG. 4A.



FIG. 4B.



FIG. 4C.

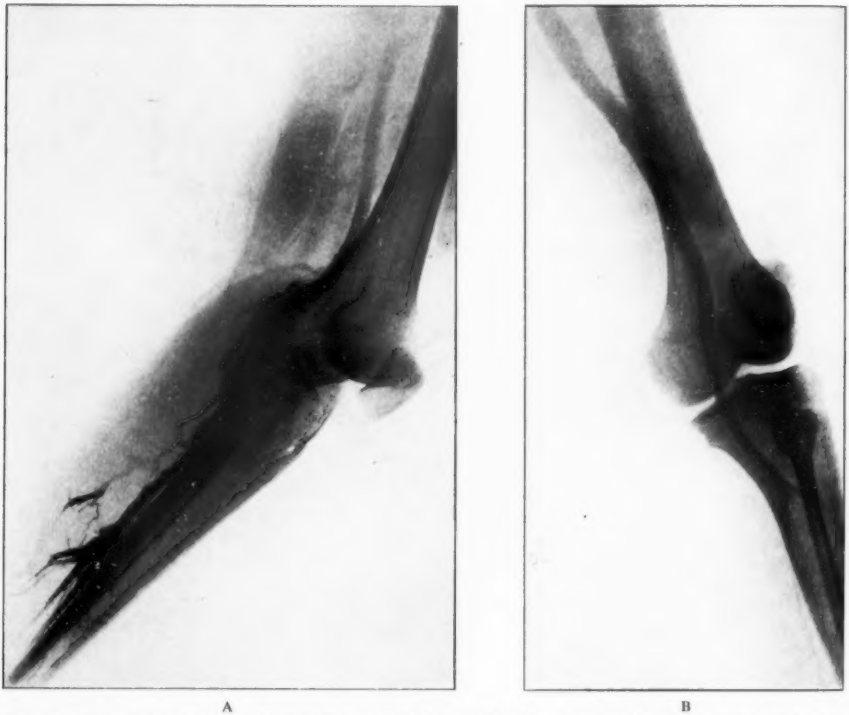
FIG. 4.—Deep thrombophlebitis: A, iliofemoral; B, thrombosis of popliteal vein beginning at level of femoral condyles; C, Deep phlebitis: calf veins.

Ilio-femoral thrombosis as the result of trauma is uncommon. Where it does occur it is usually due to secondary spread from a traumatic deep phlebitis of the calf.

Spontaneous ilio-femoral thrombosis is rare and, when observed in men after the age of 50, is indicative of malignant disease. In 5 out of 6 cases in this series a carcinoma was seen within six months. It is important to stress the sinister significance of apparently spontaneous ilio-femoral thrombosis occurring at this age and the importance of careful investigation.

(ii) *Deep phlebitis of the calf* (252 cases).—Phlebitis of the deep veins of the calf is most commonly the result of trauma, but is sometimes seen after a prolonged period of being confined to bed. It is most common under the age of 40. Apparently spontaneous deep phlebitis may be due to fungus infection of the feet or to exotoxins such as that of *Staphylococcus aureus*. The lesion may be limited to the calf veins, or the popliteal vein may be involved as far as the level of the upper border of the femoral condyles (Fig. 4B). The proximal part of the popliteal vein appears to be relatively immune from thrombosis spreading either from the ilio-femoral segment or from the deep veins of the calf (Fig. 4C).

(iii) *Deep venous stasis* (73 cases).—In a number of patients with œdema of uncertain origin, phlebography revealed dilatation of the deep veins of the calf and absence of the usual valvular markings (Fig. 5A). This condition of the deep veins was not always confined to the calf; sometimes the popliteal vein appeared dilated with a smooth outline suggesting complete absence of valves (Fig. 5B). Progressive loss of valves leading to varicosities of the calf veins and deep venous stasis may be the cause of many of the œdemas classed as "of unknown origin".



A B

FIG. 5.—"Smooth" veins. A, dilated and smooth deep calf veins; B, smooth and apparently valveless femoro-popliteal veins.

(2) *Erythrocyanoid*

There were 168 cases of erythrocyanoid œdema in the present series. Under this heading are included erythrocyanosis frigida, and the cold cyanosed swollen limb sometimes seen following infantile paralysis. Mild degrees of erythrocyanosis frigida are exceedingly common; in severe cases the primary complaint of the patient may be the swelling of the leg.

(3) *Lymphœdematous*

In this series there were 69 cases listed under this heading, 11 being of inflammatory and 58 of unknown origin.

The cases of lymphœdema of inflammatory origin presented a similar history of recurrent streptococcal infection and subsequent lymphatic obstruction.

Patients having lymphœdema of unknown origin were mainly unmarried women between the ages of 20 and 30 years. The swelling was bilateral though often more advanced in one limb. In the early cases the swelling pitted on pressure and disappeared with elevation; in those of long standing pitting was less marked and there was little reduction of swelling with elevation. The absence of pain distinguished these cases from the post-phlebitic group. Phlebography often showed smooth valveless veins suggesting that the original cause may have been deep venous stasis.

There were no cases of filarial lymphœdema.

Treatment

In all types of œdema there is an early reversible stage during which the condition can be cured or at the worst held in check. The principles of treatment at this stage are mobilization of fluid; prevention of accumulation of fluid in the dependent limb; removal of the causative factor where known. Neglect of these principles leads to the irreversible stage.

Management During the Reversible Stage

Details of treatment depend on the results of careful investigation but in all cases preliminary treatment consists of bed rest with the legs elevated on a wedge mattress. The degree of subsidence demonstrates the extent of permanent damage. Where there is rapid and total disappearance of the fluid on elevation, complete cure should be possible. Where, however, reduction is incomplete resolution may still take place over a period of time after correcting the circulatory defect.

Before logical treatment is possible an accurate assessment of the arterial and venous circulation is imperative.

At present the only available method of correcting deep venous stasis is ligation of the main vein thereby interrupting the column of blood. The optimum site of ligation is still a matter of discussion; Linton (1948) prefers the superficial femoral vein immediately below the femoral valve, while Gunnar Bauer (1950) prefers the popliteal vein. Phlebography shows the site and extent of the lesion and the degree of competence of the principal valves. The phlebographic findings were confirmed by the change in venous pressures on exercise. The main consideration of the site of the ligature should be the state of the valves, ligation being carried out at the level of the highest incompetent valve. Generally this implies ligation of the superficial femoral vein in old cases of ilio-femoral thrombosis and the popliteal vein in deep phlebitis of the calf which has extended proximally to destroy the popliteal valve.

In our series the results of main vein ligation have not been encouraging. A material reduction of the swelling has only been seen in a few instances and some have actually been made worse. It is only fair to state that the early ambulation advocated by Gunnar Bauer and Linton has not been carried out in the majority of cases. Certain patients, whose main complaint was a "bursting" pain in the calf, were relieved by the procedure.

Sympathectomy

It seems possible that some of the symptoms of deep phlebitis, including œdema, are due to vasospasm interfering with arterial inflow and the development of collateral channels. The vasospasm may be removed by lumbar ganglionectomy.

On logical grounds it might appear that certain cases, where there is little evidence of vasospasm, might be made worse by sympathectomy resulting indirectly in over-dilatation of the veins. In practice this has not been found to occur.

In our series the majority of successful results belong to the group in which sympathectomy was carried out either alone or in combination with other procedures.

In our opinion sympathectomy should always be performed on the erythrocyanoid type. Ulcers are healed or prevented and general improvement occurs in the nutrition of the tissues. Swelling, however, is little affected.

Whatever method is adopted it is essential to control the œdema in the dependent leg in the post-operative period until resolution takes place. The importance of elastic compression during this time cannot be over-emphasized.

Management in the Irreversible Stage

The irreversible stage is characterized by thickening of the deep fascia and fibrosis of the subcutaneous tissues as a result of persistent œdema. Pockets of fluid are found among the fibrosed tissues, giving the typical appearance seen on soft tissue X-rays.

The existence of this deplorable condition should serve as a warning of the absolute necessity for immediate and adequate treatment in the reversible stage.

In this late stage treatment must be directed to prevention of further deterioration by the use of elastic compression and by the careful avoidance of all types of infection of the skin owing to the proneness of the condition to recurrent cellulitis leading to lymphatic obstruction.

In certain cases removal of the affected subcutaneous tissue may become necessary. The indication for a modified Kondoleon operation is when the limb becomes heavy and painful, the wearing of shoes impossible, and ulceration of the skin imminent. The operation carried out in our series has been that described by Poth, Barnes and Ross (1947). It is too early to evaluate the results.

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Professor Ian Aird, *Department of Surgery, Postgraduate Medical School of London.*

Chronic lymphœdema is an obstinate and difficult condition which still requires extensive investigation. Its ultimate treatment will doubtless make our present methods completely obsolete.

Surgical measures should be reserved for solid, non-pitting œdema. While every chronic non-pitting œdema is the result of a previous pitting œdema, not every chronic pitting œdema proceeds to a solid form. The ultimate state of a non-pitting solid œdema has been well described. Superficially under the skin is a honeycomb of watery lymphatic spaces. Deep to this again is a layer of fibroblasts increasing in cellular density when followed deeper until on the surface of the deep fascia, and forming one mass with it, is a layer of dense mature fibrous tissue. In due course even the most superficial layers of the superficial fascia are replaced by a solid fibrosis (with complete loss of all pitting) which may replace also the skin, and this may be pocked like an orange-rind, hard and inelastic, thickened, and sometimes inflamed and ulcerated.

The reason why some œdemas progress to solidity while some remain pitting after prolonged chronicity is not fully understood. The watery varieties of cardiac or renal œdema do not become solid even in the relatively infrequent cases in which they present long enough to render solidity possible. For solid œdema to persist, a relatively high concentration of protein must be present in the œdema fluid. This is likely to attain its highest level when the fluid in the tissue spaces is lymph, as it is in cases of complete lymphatic obstruction—filariasis, for example, and malignant elephantiasis. The faculty inherent in lymphatic obstruction to stimulate fibroblast proliferation is taken advantage of in pulmonary tuberculosis; one effect of collapse therapy is to close off lymphatic channels and so encourage fibrosis. The protein content of hepatic œdema fluid is sometimes high, but hepatic failure severe enough to produce œdema is too rapidly fatal to allow a solid œdema to supervene. The œdema of protein deficiency too is cured or proves fatal before it can produce an irreversible fibrous change.

In the early stages of pitting œdema, conservative methods alone are required, to disperse the watery œdema and to prevent its progression to a solid form. Some consideration must be given in this earlier stage to the cause of the œdema, for some forms of œdema lend themselves to additional specific forms of therapy.

(1) *The congenital variety* of the disease, first described by Milroy, is seldom seen in its pitting stage, even though its onset is sometimes delayed for years, and treatment, if it is applied at all, must be surgical. A diagnosis of Milroy's disease, incidentally, should not be made unless there is evidence of inheritance.

(2) *Chronic lymphœdema* may sometimes be related to congenital arteriovenous fistula. Typically this gives increased length of limb—but only if the fistula lies on the main vessel of the limb proximal to a nutrient artery, or on the nutrient artery itself or one of its branches. In one case a warm and increasingly œdematous limb, with an œdema partially solid and unrelieved by elevation, was associated with multiple cutaneous nævi. The flow in the limb was high. Certain of the nævi were excised for microscopic examination without improvement of the œdema—nor would one expect it. The fistulous communications in such a case are probably very numerous.

(3) *Post-traumatic lymphœdema* may or may not be associated with Sudeck bone atrophy. It is notable that when the two conditions are associated the bone atrophy extends proximally strictly to the level of injury, while the œdema extends proximally just as it does in other forms. In this form of lymphœdema more than in others it is safe to depend upon "Time, the Healer", provided in the meantime the pitting œdema can be prevented from proceeding to a solid form. In this as in most other forms of lymphœdema sympathectomy is ineffective, though the natural tendency of the condition to heal makes sometimes for falsely congratulatory assessment.

(4) *Lymphœdema artefacta* is a foil for the brave, as it too can proceed to an irreversible solid form. The sharp upper border, the constriction groove above it, and the high level of greatest diameter, just below the groove instead of the lowest dependent part, should assist in diagnosis. The application of a whole limb plaster will not necessarily cure, but it will raise the level of the upper line of the œdema, and prove the diagnosis.

(5) Of the *filarial* form of the disease I have little knowledge though I have often admired the comfortable portable scrotal shop-counter of the peanut-vendor in a famous textbook of tropical medicine.

(6) *Post-thrombotic lymphœdema* can be prevented by the effective conservative treatment of venous thrombosis for a period of a year. It seems reasonably certain now that this form is due, in part at least, to valvular incompetence in recanalized venous thrombus, and, if this is proved by phlebograms, ligation of the femoro-popliteal trunk is helpful in treatment.

(7) The *lymphœdema of erythrocyanosis frigida* has been fully considered by Professor Boyd in his notable original work (*see* p. 43).

(8) The *infective form* of lymphœdema begins with a succession of attacks of cellulitis, erysipelatous usually. This form is probably not due to lymphangitic obstruction of lymph pathways so much as to the persistence, after the first attack, of fixed local antibody in the affected area. It is a local form of streptococcal allergy. This explanation is implicit in the distribution of the œdema, which is not strictly gravitational, but is maximal in relation to that skin area which is subject to the attacks of inflammation. A special form of treatment may have some value here—forcible massage of the area during an acute attack under penicillin and streptomycin cover.

(9) The *angioneurotic form* of chronic lymphœdema—Quincke's disease—may proceed to a solid form, though it seldom does so in the legs. It is most extreme and most pathetic in its typical sites of tongue and lip. When it does occur in the leg it resembles the infective variety in not becoming purely gravitational until it reaches a late stage, and the toes sometimes escape, as they never do in gravitational forms. It is differentiated from the streptococcal variety by the great speed with which its acute exacerbations develop. This variety does not, in my experience, improve much after sympathectomy though, like the two previous varieties, it has a tendency to natural cure after one or two years. It is in this variety, due presumably to the effect of fixed local antibody upon capillary permeability, that we have most to hope from anti-histamine drugs. There is not yet available, however, any chemical agent which will reverse acute angioneurotic œdema with the dramatic rapidity of its onset.

The recurrent and chronic œdema of insect bites, and of drug reactions (I have seen a local œdema of chest wall in a susceptible female persisting for weeks after the distant intravenous injection of an iodine compound) behaves in a similar fashion. Perhaps the œdema provoked in some women by nylon and silk stockings is of a similar nature.

(10) *Lymphœdema præcox*, spontaneous lymphœdema, the chronic œdema of puberty as it is called though it may arise at any time during the child-bearing age, is the most progressive and intractable of all lymphœdemas except the malignant. Starting in foot and ankle, and rising slowly to the groin, first unilateral but ultimately after a few years following the same sequence on the other side, must be due, too, to a local allergic effect—no obstructive process could symptomlessly occlude *all* the lymph vessels of an extremity after two or three decades of normal lymphatic drainage. In many cases of this variety incompetence of deep veins can be shown to be present, even if there is no history of phlebitis.

(11) The *malignant* variety of lymphœdema of the lower extremities is a notorious pitfall. To excise the œdematous subcutaneous tissue from the lower extremities, overlooking a malignant prostate, is less excusable only than performing the same operation for undetected renal or cardiac œdema. Abdominal and rectal examination should not be omitted in any case. The malignant pelvic *lymphatic web of Guyon* is the commonest cause of this variety of lymphœdema, most usually of prostatic origin. Sometimes skin nodules round the waist furnish a presumptive diagnosis or material for microscopy.

(12) The *post-operative and radiation lymphœdemas* are difficult to distinguish from the malignant, for two or three of these causes are usually present together. A hospital porter had the left testis removed for seminoma nearly six years ago. Large malignant abdominal masses present at that time disappeared under irradiation. He developed an ilio-femoral thrombosis on the same side as the tumour, and a lymphœdema which persisted for three years with extensive ulceration. I regret that there is no pictorial record of the lymphœdema during its active stage, but our most recent photograph (all signs of tumour have disappeared) shows the sole remaining testis, the pigmented area of irradiation, and a left leg which is now visibly smaller than the right. This encouraging result was obtained under ambulant working conditions by vigorous bandaging with elastic web. It shows that an œdema due partly to malignant and irradiation lymphatic obstruction, partly to venous thrombosis, can be corrected by pressure even against gravity. The narrow diameter of the limb reflects the atrophy which always affects the muscles deep to a lymphœdema and which appears to be permanent.

Summary.—In chronic œdema, whatever its cause, one's best hope lies in controlling the œdema while it is still of a pitting kind, by elastic bandage (and preferably bedrest) initially, and elastic stocking later. I believe that the elastic stocking should extend to the groin and be supported by a suspender belt. A patient who wears a knee-length stocking too often develops an ugly roll of œdema above it. The stocking is continued in post-traumatic and post-thrombotic cases for a year or so, in angioneurotic and inflammatory cases for so long as attacks occur, and in other cases for life. Sympathectomy has, in my hands, had a limited and doubtful success in angioneurotic and post-traumatic varieties and no success in other forms.

Solid œdema can be relieved only by operation. I believe that two-stage excision of whole thickness of subcutaneous and deep fascia after elevation of thin rectangular flaps hinged medially and laterally is the operation of choice. At the first operation a median anterior incision with upper and lower cross-pieces is used at the first stage, the anterior surface being dealt with from the knee to the bases of the toes. The posterior aspect of the calf is dealt with at a subsequent session three or four weeks later.

The aim of this operation is the removal of the fluid extracellular space of the subcutaneous tissues; it is based in fact on an entirely different principle from that of Kondoleon. The wide sacrifice of cutaneous nerves is not important; sensation regenerates centripetally from the periphery and is adequate over the whole area in rather more than a year. The only undesirable feature of the treated limb is the ugly swelling of the toes.

If the skin of the affected part is adherent to underlying fibrous tissue, or ulcerated, or attenuated, or all of these, then flaps cannot be formed and skin grafts must be placed on the underlying muscle after excision of the atrophic skin together with the subcutaneous tissues, by the technique which has proved so satisfactory in the hands of Sir Archibald McIndoe and his colleagues.

Amputation is much more seldom necessary for elephantiasis of the leg than for elephantiasis of the arm consequent upon excision or irradiation of a malignant breast, and for four reasons: (1) The lymphatics of a lower extremity are not collected in the bottle-neck which the surgeon, the radiologist, and the disease find so readily to hand in the axilla; (2) the femoral vein is less likely to be damaged by an operation on the groin than the axillary vein—and the cephalic—in a breast excision; (3) it is more convenient, curiously enough, to keep the leg elevated than to keep the arm elevated, and (4) block dissection of the groin glands is not nearly so commonly necessary as the glands in radical amputation of the breast.

Sir Harold Gillies, London: *The Lymphatic Wick.*

Miss C. T. Case was reported in the *British Medical Journal* in January 1935 (i), 96, by Professor F. R. Fraser and myself. The case was also shown clinically at the Royal Society Medicine (McIndoe, 1935, *Proceedings*, **28**, 1118).

Summary of the case.—Bilateral lymphœdema of the legs of long standing. Five years of expert and persistent medical treatment and two Kondoleon operations had not materially relieved it. The question of amputation arose.

A new principle was adopted as a radical cure, i.e. the implantation of a lymphatic wick from the thigh to the axilla so by-passing the block in the iliac vessels. The operation is not indicated except where a definite block can be diagnosed in the iliac region. It is applicable also to a lymphatic block in the axillary or any other region (Fig. 1).

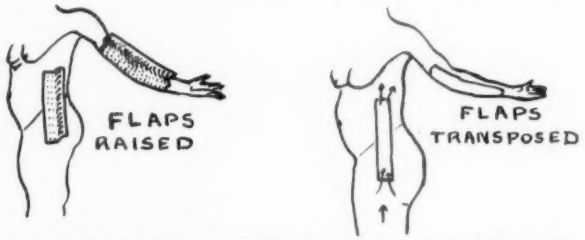


FIG. 1.—Design of the operation (from *Brit. med. J.*, 1935 (i), 98).

The donor graft was designed from the inner aspect of the arm and forearm. In this strip of skin a large number of lymphatic vessels run. In order to prove beyond doubt that the lymphatics of the arm can drain the lymphatics of the thigh and so reduce the œdema, the left arm was joined to the upper part of the thigh and retained there for some weeks. The œdema went down markedly on the left leg, even when the patient got out of bed. A strip of skin was subsequently divided from the arm and embedded into the abdominal wall, stretching from below Poupart's ligament to the lower part of the axillary drainage. That lower limb, and subsequently the right, which was treated similarly, have remained free of lymphatic œdema for fifteen years (Figs. 2 and 3).

A very interesting sidelight occurred in connexion with the investigation. The late Professors Woollard and Gray injected thorotrast with the idea of seeing how this lymphatic anastomosis had developed. These masses have subsequently been surgically removed, and caused a good deal of anxiety.

It was considered at one time that the catchment area of the lower end of the right flap was not sufficiently low or spread, so a second flap was taken off the right forearm and added to the previous one completing an excellent drainage of the right thigh.



FIG. 2.—The legs in 1934.





FIG. 3.—The legs in 1949.

The right wrist remained perfectly normal and the hand non-œdematous until the thorotrast apparently picked out the last remaining lymphatic vessel and after that date the hand was very materially troubled with œdema. Demonstrating still further the value of this "lymphatic-wick" principle was the subsequent cure of this œdema. A piece of skin from beneath the right breast was designed as a flap, having its lymphatics running upwards towards the right axilla, and that was implanted over the back of the wrist and so again bridging the lymphatic block by means of a lymphatic wick. That hand has remained practically normal (Figs. 4 and 5).

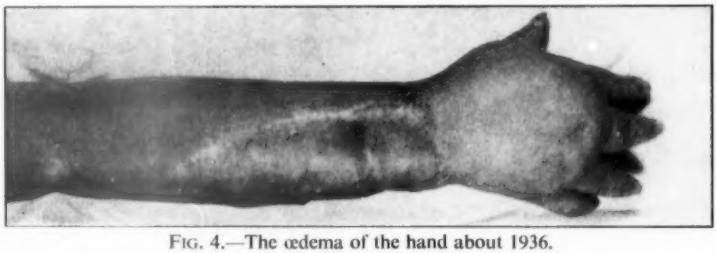


FIG. 4.—The œdema of the hand about 1936.

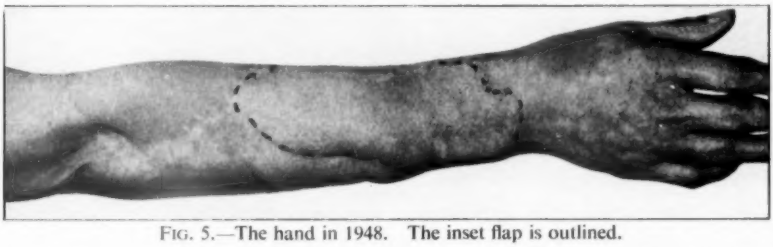


FIG. 5.—The hand in 1948. The inset flap is outlined.

After some partial successes and some rank failures it became obvious that some further modification of the original technique was desirable. The tube pedicle method had been first used on the patient's right leg and was further elaborated by Mowlem. Gray, working at my suggestion, worked out an anatomical scheme by means of which the subcutaneous

tissue of the forearm could be removed without the skin and implanted as a free graft tunnelling the abdominal wall from the axilla to the saphenous opening. At each end this composite lymphatic vessel graft was divided into strips so as to get as big a catchment area as possible. The operation has, unfortunately, only been done on the one occasion and that on a case that was totally unsuitable for the operation; and the value of this very hopeful procedure cannot therefore be assessed until some surgeon has done a whole series of them.

I feel that a limit in the palliative type of operation has almost been reached, and that further progress can be made only by persistent research on the lines of the lymphatic wick. A trouble-free method of demonstrating small lymphatics would obviously help this research.



FIG. 6.—The first and second flaps for the cure of the right leg. The donor area of flap for cure of wrist is also seen. (Sir Harold Gillies' case).

Mr. A. J. Walker, *St. Bartholomew's Hospital, London:* Although the diagnosis of swollen legs of venous origin may be suspected from the history, rational treatment should be based on venous pressure measurement and phlebography. In my method, a fore-foot vein is cannulated with a polythene tube filled with heparinized saline which passes into a half-filled reservoir in which the pressure is adjustable and readable on a mercury manometer. To read the venous pressure, the pressure in the apparatus is raised above the expected venous pressure and lowered very slowly. When blood appears in the polythene, the manometer is read. The flexibility of the polythene allows readings during exercise. The resting pressure always corresponds to heart height, but in deep venous incompetency, the pressure on exercise lies between 50 and 110 mm.Hg, unlike the normal of under 30 mm.Hg. Exercising with a light tourniquet below the knee produces no change in the pressure, unlike varicose veins when the pressure falls to normal. Patency of the deep veins is shown by ascending phlebography, but if definition is poor, phlebography is repeated from the popliteal vein. If the main vein is patent and incompetent as shown by the pressure readings, like Bauer (1948) I tie the popliteal vein. Bursting pain, cramps, pain of ulceration are regularly relieved by this operation, but of 17 œdematous limbs, in only 2 did the œdema disappear, while in 5 others it became controllable by elastic support. In 3 cases it became worse. To exclude cases not likely to be improved, I now refuse ligation to patients with œdema, eczema or ulcer, in whom the venous pressure is not lowered by exercise.

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Dr. A. H. Ratcliffe, *Department of Surgery, Manchester:* Analyses have been made of serum and tissue fluids, but from the research point of view the results were "depressingly normal". The fluid in the limb may be described as afferent vascular, extravascular, and efferent vascular; the relationship determines the existence and extent of the œdema. The total protein content of the extravascular fluid was usually about 0·5%, rarely was it above 1%. The only positive finding which may be of interest was that the albumin-globulin ratio was either high or the same as in the serum. The former was perhaps attributable to imbalance between the afferent vascular and extravascular fluids and the latter to impaired protein re-absorption.

Mr. S. S. Rose, *Department of Surgery, Manchester:* There are two methods of investigation which have been helpful in our approach to the swollen leg problem. The first is the soft tissue X-ray.

We have found that a very typical pattern can be observed in the soft tissues—dependent on the increase in thickness of the fibrous tissue septa and fascia, which we have all observed at operation, X-rays of the normal soft tissue of the heel which we know to consist of a fibrofatty pad show a similar appearance. Furthermore the pattern seems to take some time to develop. The œdemas of recent origin, e.g. of one to two years' standing, show at first a diffuse, comparatively fine bubbly appearance and later a much coarser, wider meshed network, the framework of the mesh becoming much thicker (Fig. 1).



FIG. 1.—Soft tissue X-ray. Patient suffering from chronic lymphœdema of the left leg for ten years. There is marked fibrous trabeculation.

FIG. 2.—Soft tissue X-ray. Venous œdema of two years' standing, showing a diffuse enlargement of the limb with normal relationship of tissue strata and no trabeculation.

I think the changes run parallel to the ease with which pitting may be elicited on pressure, the longer standing cases of swelling being due more to the actual transformation of œdematous tissue into a fibrofatty mass containing little free fluid. Œdemas of recent origin, e.g. cardiac, show merely a diffuse ground glass opacity with obliteration of muscle tendon and fascial outlines.

A further point of distinction arises in comparison of venous and so-called lymphatic œdemas. Apart from the comparative lack of mottling in the venous œdema (Fig. 2), the swelling is distributed evenly through the whole leg, as opposed to the gross increase from the deep fascia outwards in the "lymphatic" type.

The second method used has been an attempt to estimate the circulation in the tissue fluid of an injected radio-opaque water-soluble substance—with the idea of investigating the effects of lymphœdema on this circulation. The method has proved to be harmless and, when combined with 2% procaine, painless. The technique is simple; a solution of 35% Pyelosil with 5 c.c. of 2% procaine is injected subcutaneously in the outer side of the calf; the site is marked and serial X-rays are taken after the subject has walked about during the period of investigation. The distance of the spreading edge from the injection site is measured.

The results in a normal leg illustrate rapid diffusion over the space of two hours, more upwards than downwards. All the dye had gone in $3\frac{1}{2}$ hours.

We are not yet in the position to make categorical statements about our results but we have sufficient evidence to suggest that this method of investigation will prove to be most valuable.

Mr. Peter Martin, *London:* The changes which occur in lymphœdema, particularly when there have been recurrent attacks of infection, are irreversible. Microscopically, in an advanced case there remains little of the normal fatty tissue, most of this being replaced by a dense fibrous tissue. Excision of all the tissue between the dermis and the underlying muscle removes the disease, and is accompanied by relief from the recurrent inflammatory attacks with their rigors and severe general symptoms. I have carried out this operation in four limbs using flaps hinged on the subcutaneous border of the tibia and on the mid-line posteriorly cut as thinly as possible, and subsequently stitched back in position and covered with pressure dressings. The appearance of the limbs following operation is bad, but the patients are relieved from their disabling attacks, and, so far, they are all pleased with their relief. The subsequent appearance of the limb can be disguised to a certain extent by wearing an elastic stocking padded with wool.

Mr. Michael Oldfield, *Leeds:* At present, the exact cause of chronic lymphœdema of the legs remains obscure in the majority of cases. Probably owing to this, the various operations designed for the treatment of moderate and uncomplicated lymphœdema are usually followed by disappointing final results: Sistrunk's modification of Kondoleon's operation only reduces the size of the leg temporarily. Therefore in the present unhappy state of our ignorance, conservative treatment by elastic bandages, raising the foot of the bed at night and massage, should be advised for these patients.

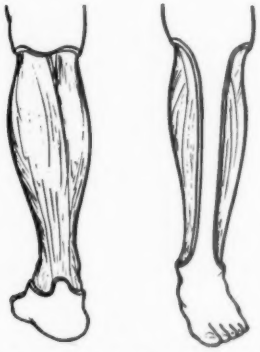


FIG. 1.—Diagram showing the area from which the hypertrophied skin, subcutaneous and deep fascia are excised. Thick, free skin grafts are applied over the muscles laid bare in this area.

When simple lymphœdema has, however, progressed to elephantiasis and the skin and fascia are gigantically hypertrophied, the patients suffer severe pain and are unable to walk. Active surgical treatment under these circumstances cannot be denied, because the patient's legs have reached such a monstrous size and are useless for walking. The operation should be radical: the whole of the hypertrophied skin, subcutaneous and deep fascia, except for a strip over the shin and tendo achillis, should be excised from knee to ankle. The bare muscles should then be covered by free skin grafts (Fig. 1). This procedure, described by Poth *et al.*



FIG. 2A.



FIG. 2B.



FIG. 2C.

FIG. 2.—Photographs showing the effect of Poth's operation in a patient suffering from severe lymphœdema and elephantiasis of the leg.

and Mowlem, results in an ugly thin leg, but one which is efficient for walking (Fig. 2). In my experience the use of local skin flaps, however thinly they are cut, is followed in due course by recurrence of swelling.

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[*June* 23, 1950]

MEETING AT THE GENERAL INFIRMARY, LEEDS

Fibro-adenosis

By H. J. B. ATKINS, D.M., M.Ch., F.R.C.S.

IN this short paper I shall make but one point in regard to the disease fibro-adenosis, and try to establish from that point one corollary. This corollary does not appear to have been made hitherto or, if it has been made, has not been much emphasized.

Fibro-adenosis is the disease which is often described as "chronic mastitis". When we define fibro-adenosis as a disease in which the breast is painful and nodular, but in which this painful nodularity is not due to neoplasm, bacterial inflammation or fat necrosis, we are faced with the realization that an unknown, but considerable, proportion of women in civilized countries suffer from the disease. Hundreds of thousands of women complain of pain in the breast before the menstrual period, and in most cases the breast is more nodular than the surrounding subcutaneous fat. As soon as I became interested in this disease and started the Mastitis Clinic at Guy's Hospital in 1936, this fact was at once apparent. I therefore took 7 cases from the "Mastitis Clinic", M, and 7 cases from the general wards of the hospital, C, and mixed them up together giving each a code number. I then asked Mr. E. C. Hughes, at that time senior surgeon to Guy's Hospital, to examine the breasts of these women and to arrange them in order of severity of nodularity, and this was the order which he produced.

M, C, M, M, C, C, C, C, M, M, M, C, M, C.

It is true that I had not chosen from the Clinic any patient who had a definite lump, and it is true too that nodularity is on the whole more conspicuous amongst the patients attending the Clinic than in the general wards of the hospital, but clinically speaking, this is a disease without a "beginning point".

If we admit that clinically there may be no beginning point, can we be sure that histologically fibro-adenosis has a well-defined picture? Dawson has divided the epithelial changes occurring in this disease into "adenosis", where the glandular elements are multiplied, and "epitheliosis" where the epithelium within the ducts proliferates. In the "normal" breast there will be one or two alveoli seen in an average field from a section of breast tissue at a magnification of 120; in adenosis the whole field will be filled with alveoli. Between the two there is an infinite gradation, but where are we to draw the line? It is rarely indeed that we can "draw lines" that precisely outline natural processes, and in this instance it is quite impossible. Histologically in regard to adenosis then, fibro-adenosis is a disease equally without a beginning point.

The changes of epitheliosis appear with great frequency in the biopsy specimens taken from patients with fibro-adenosis. On the other hand, if specimens are taken from the breasts of women who come to post-mortem examination, and in whom it is known that no complaint was ever made about the breasts during life, these very changes appear with striking, though perhaps not with such regular, frequency. By this I do not wish to imply that the disease fibro-adenosis is not an entity, but it is, nevertheless, a disease without a well-defined "beginning point" both clinically and histologically.

We are informed from many sources that cancer follows fibro-adenosis x·y times, or even a·bc times as commonly as in the normal population. But we may well enquire, "Who *are* the normal and which are the patients suffering from fibro-adenosis?" This disease, although when well developed it is capable of being recognized both clinically and histologically, is but an aberration of the normal. It is a disease which is incapable at present of precise definition, and, this being so, it is unscientific and indeed misleading to try to reduce to mathematical exactitude a relation (namely the one between fibro-adenosis and cancer) which cannot be so expressed.

The problem of epithelial proliferation in the walls of cysts has a direct bearing upon the genesis of cancer in this disease. We shall see that cancer follows fibro-adenosis as a rare event and various factors may well contribute to this. I believe that the fibrous tissue reaction of fibro-adenosis is important in restraining epithelial growth—certainly when this fibrous tissue reaction is absent, as in the so-called fibro-adenosis of the breasts of mice induced by the injection of œstrogens, this tendency is far stronger. But other simple mechanical factors may play a part.

When, in operating upon a case of fibro-adenosis, a cyst is punctured and this ruptures with the force of an explosion, the epithelial lining of such a cyst is always flat, pavement in type and inert. No epithelial projections occur—no papillomata and no carcinoma. The cyst is quite innocent. May it be that the considerable hydrostatic tension in such a cyst acts as a mechanical restraint upon epithelial growth?

Approached from the opposite point of view, we find that where visible papillomata grow into a cyst the hydrostatic tension is low and the cyst is lax. Now cysts are lax for two reasons. First where the processes of absorption are in excess of those of accumulation, and secondly in certain cyst-like spaces near the nipple, where the accumulated products are able to discharge themselves because the space is still in continuity with a short length of duct leading between it and the nipple orifice.

The histological pictures producing on the one hand cystic fibro-adenosis, and on the other discharge from the nipple, are indistinguishable, but cancer follows the former only in the rarest instances, whereas statistical evidence is fast accumulating that the symptom of nipple discharge, whether coloured or colourless, is not to be lightly disregarded. Nipple discharge in fibro-adenosis adds to our anxiety. Here then we have another pointer indicating a relationship between epithelial growth and mechanical tension. In those cases where a "safety valve" (one might almost call it a "danger valve") is provided so that discharges appear at the nipple and intra-luminal tension is not allowed to rise, the stage is set for epithelial proliferation. The nature of that proliferation, if and when it occurs, determines the nature of the discharge. We divide these discharges into coloured and colourless (or straw-coloured) discharges. The former are subdivided into those in which the pigment is due to hæmoglobin or one of its breakdown products—an "oxidase-positive" discharge, and those in which the pigment is "oxidase-negative", and is probably melanin. The former—the oxidase-positive discharges—are associated with epithelial hyperplasia, even sometimes with cancer, and are of more serious significance. The oxidase-negative discharges, together with the colourless discharges, are not so frequently associated with this hyperplasia, and are correspondingly of less significance. Nevertheless the continuance of such a discharge must always be a source of some anxiety and demands careful observation.

The low intra-luminal tension associated with these discharges, whatever their complexion, may be the factor which allows epithelial proliferation to take place.

But to return to our main theme.

The problem as to what we are going to do when faced with a patient complaining of a painful nodular breast is based on our practical experience. If the diagnosis is certain—if in fact there is no discrete lump, the nature of which must always be in doubt—the best thing to do is to watch the condition. Out of nearly 250 cases of fibro-adenosis studied at the Mastitis Clinic since 1936, only 2 have developed cancer during that period. These histological pictures may reveal a cancerous tendency but, if so, it is a very weak one, and may be "propitiated" by watchfulness.

The corollary that I wish to draw then is that in studying this relation between cancer and fibro-adenosis, figures must be eschewed. There is a tendency to feel safe—and scientific—when we have reduced a relation to figures, but this feeling of security may be quite false and when we are dealing with a disease of such hazy outlines as this, any attempt to make a precise statement about this relation is improper, and may lead to excessive anxiety or unnecessary mutilation.

Johann von Mikulicz-Radecki (1850–1905): Pioneer Surgeon

By W. R. Bett, M.R.C.S., L.R.C.P.

Surgery recognizes no boundaries, for it is international in the truest sense of the term. It is fitting, therefore, in the centennial year of his birth to pay tribute to the memory of a great Austrian surgeon who to this day continues to be eponymously honoured in the English surgical literature and throughout the civilized world. It is fitting, too, that such tribute should be paid within the walls of an institution with which the name of Lord Moynihan will in perpetuity be so intimately and so proudly linked. For Moynihan all his professional life was a discriminating contemplator of the past, applying its lessons to the present and, indeed, to the future. He, too, was an international surgeon in the truest sense of the term, an apostle of international surgery. Equally at home in Britain, on the Continent of Europe, and in the Americas, his nimble mind was ever ready to embrace other men's ideas and to incorporate them in the art, the science, and the ritual of his daily work.

Johann von Mikulicz-Radecki was born a century ago, on May 16, 1850, in Bukovina, which was then part of Austria-Hungary. His father's family came from Lithuania, and his mother's from Prussia. He studied medicine at Vienna under such giants as Hyrtl, Rokitansky, Hebra, and Billroth. He helped to pay his fees by giving lessons on the piano

and playing the organ from 5 to 8 a.m. After taking his degree in 1875, he became assistant to Billroth, who appears to have been primarily attracted by the young man's devotion to music. Mikulicz visited Lister in 1879 and was ever after his loyal disciple and ardent evangelist.

The main events of his life can be briefly chronicled.

In 1882 he was appointed to the Chair of Surgery in the University of Cracow where he lectured in Polish, and eight years later began his long association with Breslau, where his clinic became a Mecca for surgeons from many lands. His end was tragic, for he died at the early age of 55, on June 14, 1905, of a disease in the surgical treatment of which he had been a pioneer. In December 1904 he had realized that he had a malignant tumour of his stomach. An exploratory laparotomy, however, performed by von Eiselsberg, showed this to be too firmly attached to the pancreas to permit of removal.

Contributions to surgery.—Few men have left their mark on the whole field of surgery as Mikulicz has done. His name is linked with diseases, with operations, and with instruments.

Mikulicz's disease.—Mikulicz reported a case of chronic symmetrical hypertrophy of the lacrimal and all the salivary glands in 1888, which he published, with a review of other cases, in a volume dedicated to his master Billroth in 1892 [1]. Little additional knowledge has meanwhile been acquired of this rare, obscure disease, and to-day we stand exactly where Mikulicz left off more than half a century ago.

Mikulicz's colectomy.—In 1903 Mikulicz perfected a procedure for resection of cancer of the large intestine by a two-stage or exteriorization method, which he considered the operation of choice because of its safety [2], and which Gordon-Taylor has described as "the most monumental milestone in the onward progress of colonic surgery" [3].

Mikulicz was the first to make a plastic reconstruction of the œsophagus after resection of its cervical portion for cancer in 1886 [4], and the first to use the electric œsophagoscope invented by Joseph Leiter in 1880. He himself invented the kentrotribe—an instrument for crushing an intestinal spur in artificial anus. In the field of orthopædic surgery he devised an operation of osteoplastic resection for disease of the tarsus [5] and wrote on treatment of the fractured patella in the Lister number of the *British Medical Journal* [6].

Father of the surgery of safety.—Throughout his career Mikulicz-Radecki by example and by precept strove to make surgery safer for the patient, so that, like Halsted in the United States of America, he may justly be styled the Father of the Surgery of Safety. He was one of the first surgeons in the world to wear cotton gloves while operating, with the object of eliminating himself as a source of sepsis. Halsted later introduced rubber gloves in 1890; and for the sake of historic accuracy it may be recalled that his idea had been merely to protect the hands of his favourite operating-room nurse from the strong mercuric chloride solutions extensively used in those days. Mikulicz also designed a gauze frame to cover the mouth and nose of the operating surgeon, and he made important observations on the use of iodoform in wound treatment and in surgery. He constantly stressed the danger of giving a general anæsthetic to a patient with a hæmoglobin below 30%. As an operator he was bold, resourceful, and dexterous. With Naunyn he edited the *Mitteilungen aus den Grenzgebieten der Medizin und Chirurgie*, and with Bergmann and Bruns the *Handbuch der Praktischen Chirurgie*.

The Man.—It remains to recall a picture of Mikulicz-Radecki the man. Few could claim to have known him well, despite his somewhat stereotyped charm. A tremendous worker, he appeared perpetually young both in years and in mind, and no one had ever seen him tired. He had a small, fine head, striking eyes, and exceptionally small and exquisitely fashioned hands. As critical of himself as of others, he was apt to be exacting and difficult to please.

In the centennial year of his birth Johann von Mikulicz-Radecki is gratefully remembered not for the individual contributions alone with which he has enriched the science and the art of surgery. He is gratefully remembered because in surgery the Man is greater than the Thing he creates.

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Treatment of Open Digital Injuries and the Training of Dressers in Tissue Craft

By PATRICK CLARKSON, M.B.E., F.R.C.S., and DENNIS C. DEUCHAR, M.B.

THIS paper discusses two related problems: first, how to improve the treatment and results obtained for open digital injuries, and secondly the training of dressers in tissue craft.

We have attempted a single solution for these two problems, and to indicate here the results that have been obtained in the finger injuries in the terms of healing rates, and incidence of disability when this is done. It is our belief that a uniformly high standard in results of treatment for the commonest of all open injuries, those of the upper limb below the wrist, can only be obtained if every breach of surface there is given full, formal care, in accordance with the known principles of treatment for major hand injuries. This means that even the most trivial breaches of surface are given a full primary toilet, followed by a repair (under local analgesia). The repair is preceded by the excision and/or débridement, and hæmostasis. Steps in the repair are the closure (by approximation, free graft, or flap), the dressing, and the after-care. For such work to be done special accommodation and equipment must be allotted within the Out-patient Department. Two rooms are necessary: (1) the preparation room where the patient does the primary toilet himself, in 1% Cetavlon; (2) the fully equipped theatre, reserved for this work, where the dresser, helped by a nurse who is not "scrubbed-up", works, and where under supervision he can do a detailed unhurried job for every finger injury. The special equipment provided for this work is the full standard plastic set including the lightest tissue forceps, tissue hooks, Blair blades, and the finest needles and suture materials. In addition to special accommodation and equipment some extra teaching is needed. In this teaching particular use has been made of wall space to demonstrate, by repeated photographs and diagrams, each stage in every type of finger repair undertaken. The dresser therefore has immediately before him a wide selection of visual reminders of the correct technical steps for the case under treatment.

The more elaborate repairs are done in conjunction with qualified personnel; but 9 out of 10 of approximately 3,000 operations done a year in the Out-patient Accident Theatre at Guy's Hospital are done by dressers. It is suggested that the abundant clinical material which finger injuries provide in a busy hospital give opportunities for training in tissue craft unobtainable by other means. This tissue craft includes experience in the handling of delicate tissues without prejudice to their viability, in the use of plastic techniques of value in general surgery, and in the use of the light instruments, fine needles, and suture materials necessary for the surgery of delicate tissues. Such experience is of most value to the talented and keen dresser, but training in modern techniques for the commonest of all open injuries is useful to any doctor.

The performance of this work by dressers can only be justified if the results compare reasonably to those obtained by qualified doctors. In practice these injuries are too common for full attention to be given to every case by the qualified personnel available in Casualty Departments. This meansthat in most hospitals many finger wounds are treated conservatively—by application of a dressing—with or without full toilet, and without routine excision or suture.

Results in a consecutive series of 357 open digital injuries treated in three months, including traumatic amputations of the digital tip, cases of division of extensor tendons, digital nerves, and of fracture of the phalanges are as follows: During this three-month period no patient was admitted to a hospital bed for finger injury alone. In the group without soft tissue loss (80% of the total) the average healing rate was 15·3 days. All these patients then returned to their work; rather less than half were not off work at all. The injuries due to "lacerating violence" were healed (dressing and scab free) in 10·2 days; and the "compression" injuries, that is the open contusions, in 18·6 days. Infection was considered to be a significant cause of delay in 1 to 2% of cases. There were no major infections needing early suture removal in this series.

The second series concerns the results in 118 consecutive traumatic amputations of the finger tip treated in fifteen months. The simplest of methods of repair, by free grafts of thin split skin, gave the most satisfactory early results, and an average healing rate of 24 days. Other methods included re-suture of the amputated part; composite grafts of the ear lobule; thenar and palmar flaps; combined local flaps with free grafts; and proximal amputation; these together gave an average healing time of 30–40 days. A late follow-up of these amputation cases showed that all except one of the patients had returned to his original work. The thin

split-skin grafts gave stable symptomless stumps, but were of poor sensitivity and somewhat unsightly on account of their yellow colour and flatness. It is suggested that this simple method is best reserved for traumatic amputations on the medial three digits in patients to whom appearance and sensitivity of finger tips are not important. Some type of flap repair, when re-suturing of the amputated part is not practical, should be used for thumb and index finger amputations. Proximal amputation of the digit, in the absence of injuries proximal to the amputated stump, is almost always an unjustifiable sacrifice of important tissue.

In addition to the operative experience which this work affords the dressers, these results are known to be an improvement on those obtained in the Department before the institution of the plan of treatment detailed above whereby every open hand injury is given a full, formal treatment.

TRAUMATIC AMPUTATION OF PULPS OF RIGHT FIRST, SECOND, THIRD AND FOURTH DIGITS



FIG. 1.

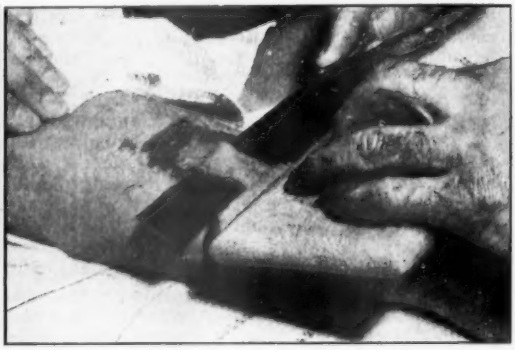


FIG. 2.



FIG. 3.



FIG. 4.

FIGS. 1, 2, 3 and 4.—Following an accident while unloading a lorry-load of glass this patient was seen with the remnants of pulps of the affected digits attached by tattered threads to the fingers. After toilet and marginal excision the 4 raw areas were covered by thin split-skin grafts fixed by sutures, dry gauze pressure, and zinc oxide strapping. The patient returned the next day, on his own initiative, to the driving and unloading of lorries.



FIG. 5.



FIG. 6.

FIGS. 5 and 6.—At first dressing a week later the grafts were an "edge to edge" take, and all finger movements were virtually full. A year later (Fig. 6) the grafts were found to be supple and non-tender, and had been stable to repeated minor trauma. They were of poor appearance, being flat and of yellowish tint. Their sensitivity was poor, with patchy areas of analgesia to pain and touch. This type of simple repair is suitable for traumatic amputations of the pulp in the hands of such patients. It can give similar results when the phalanx is involved in a stump, provided that the anterior part of the phalanx is first removed so that the pulp tissues can be approximated to the nail bed to give a uniform soft tissue bed for the graft.

Observations on the Extent of Denervation after Thoracic and Thoraco-Lumbar Sympathectomy

By MICHAEL WILSON, M.B., F.R.C.S.

AT Mr. H. S. Shucksmith's suggestion I have examined a number of patients upon whom he has performed extensive sympathectomies for hypertension, using Guttman's Quinizarin Sweat Test.

The object in the first place was to see whether or not there was any correlation between the success of an operation as a reducer of the blood pressure, and its success as a sympathectomy—judged by its effect upon the skin.

The number of cases so far investigated has not been sufficient to form any definite opinion on this score, but the sweating patterns produced are of some interest from the point of view of the anatomy of the sympathetic nervous system.

A variety of operations has been performed on these patients: some have had a purely thoracic sympathectomy, some a "thoraco-lumbar" sympathectomy, and a few have had a so-called "total sympathectomy".

Photographs of these patients (Figs. 1–10) show a comparison of the levels of section of the chain with the areas of skin affected, and also demonstrate "escape areas", that is to say areas within the scope of the expected denervation where sweating has nevertheless taken place. These areas are found most constantly across the front of the chest, and on the thighs and pubes.



FIG. 1.—Removal of thoracic chain and splanchnics left side only, T3–T12, resulting in sweat loss in small area of skin in the lower half only of the field.



FIG. 2.—Removal of thoracic chain and splanchnics on both sides T4–12. Upper arm and shoulder affected on left side only, band of sweat loss across upper abdomen and in area corresponding to L1 on both thighs. Lower level of section of cord is above L1, fibres destined for this segment probably left the cord at a higher level and were interrupted in their descent through the chain. Groins and pubes not affected. Absence of palm sweating was noticed on normal controls and does not seem to be of significance.



FIG. 3.—Right side T2–12, left side T3–11. Splanchnics. Right arm sweating only on hand, left arm sweating of hand and forearm. "Escape area" across front of chest at nipple level.



FIG. 4.—T2–12 both sides. Splanchnics. Absent sweating on trunk, diminished sweating both arms. Suggestion of "escape area" across front of chest.



FIG. 5.—T2–12 both sides. Splanchnics. Very incomplete and irregular distribution of sweat loss.



FIG. 6.—Right side T4–12, left side T9–L2 (Smithwick). On right side clean-cut area of anhidrosis representing most of segments involved. On left side partial "escape" of thigh.



FIG. 7.—T7–L3 both sides (Smithwick). This is the characteristic pattern after thoraco-lumbar sympathectomy with an area of partial "escape" on the thighs and pubes.



FIG. 8.—Right side T10–L2, left side T8–L3. (White areas on arms and upper chest are artefacts.) Escape of outer aspect of thighs and pubes.



FIG. 9.—"Total" sympathectomy. Chain removed from inferior cervical ganglion to L2 both sides Typical "escape areas" across front of chest, on both thighs and pubes, as well as the greater part of both arms.



FIG. 10.—T8–L2 both sides (Smithwick). In this case the only portions of skin which have not "escaped" are two small triangles in the iliac region and the legs below the knees. Furthermore the amount of sweating in the "escape areas" was greatly in excess of that in the intact parts of the body.

It remains now to try to explain the constant occurrence of "escape areas", across the chest and on the thighs and pubes.

Various authors have noted their occurrence, Ray and Console in 1948 "found that they were not present immediately after operation, but became manifest in from a few days to three months afterwards. They also found that they were abolished by anterior rhizotomy. In a few cases they actually combined paravertebral sympathectomy with anterior rhizotomy of T 10–L 3, and reported that there was no noticeable loss of motor function in the leg. To explain these areas of escape they deduced the existence of sympathetic pathways that did not pass through the sympathetic chain, but did not demonstrate their location.

On similar grounds Smithwick in 1936 had decided that it was necessary to divide the second and third thoracic roots as well as the chain to achieve a satisfactory sympathetic denervation of the arm.

The actual pathway taken by these "extra-funicular" fibres has been indicated in a recent paper by Boyd and Monro (1949) who have demonstrated the existence of "intermediate ganglia" behind the psoas muscle on the course of the rami communicantes or embedded in the anterior nerve roots, in the segments T 12–L 5. These ganglia and their connexions are not interfered with by removing the sympathetic chain. They probably represent cells which have dropped out in their migration from the primitive C.N.S. to the sympathetic chain.

These ganglia were first described by Wrete in 1935 who named them "intermediate ganglia". Skoog (1947) has described similar ganglia in the cervical region.

Alexander *et al.* (1949) have described aggregates of ganglion cells partially or completely embedded in the anterior nerve roots particularly in the first and second thoracic and in the first and second lumbar segments, and also of intersegmental communications outside the sympathetic chain.

While it seems reasonable to ascribe residual sweating that is diminished in amount to residual extra-funicular pathways, can residual sweating in excess of the normal, as has occurred in some of our cases, be attributed to the same cause? I think it probably can. The number of sweat glands retaining innervation is diminished, but they may make up for it by increased output. It is well known that after sympathectomy excessive sweating tends to occur in intact parts of the body, particularly in border zones and contralateral areas. A similar compensatory process may perhaps take place in the "escape areas", and occasionally raise sweating in these areas above the general level.

It seems unlikely that regeneration plays any part in the explanation of these phenomena, in view of the demonstration by Ray and Console that they may appear as soon as a few days after sympathectomy. Further, it is just in that area below the knee, where the peripheral neurone is left intact by the usual sympathectomy (which stops short at L 2 or L 3), and the gap to be bridged by regeneration would be shortest, that the escape phenomenon never seems to occur.

In conclusion, these few observations seem to show that, excepting the head and neck and the splanchnic areas, which were outside the scope of this investigation, the only portion of the body that one can be sure of denervating by operations confined to the sympathetic chain is the leg below the knee.

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The Acute Complications of Diverticulitis of the Colon

By G. W. VAUSE GREIG, F.R.C.S.

IN a series of papers Maxwell Telling (1917) established diverticulitis of the large intestine as a clinical entity. He listed the acute complications as:

(1) Inflammatory lesions in the right iliac fossa due to (*a*) Diverticulitis of ascending colon or cæcum. (*b*) Abnormal position of the sigmoid colon.
(2) Inflammatory lesions in the left iliac fossa.
(3) Pelvic abscess.
(4) Generalized peritonitis.

(5) Acute intestinal obstruction from bands, adhesions, or kinking of a loop of intestine.

To these I would add two others:

(6) Hæmorrhage.

(7) Acute vesico-colic fistula.

Of the latter complication I have no personal experience but Pyrah (1950) reports a case presenting as a severe acute cystitis with none of the usual premonitory signs of a fistula. Examples of all the other acute complications have been seen.

In the five-year period 1945–49, 72 in-patients at the General Infirmary at Leeds were diagnosed as cases of diverticulitis. Of this total of 72, 25 were admitted as "Acute"—all, excepting two, to the surgical wards: 0·2% of all acute surgical admissions.

It is with 24 of these 25 acute cases that I am concerned. One was a case of diverticulitis of the ascending colon in a man of 26, with which I shall not deal as I consider this to be a separate ætiological condition. In the other 24, the descending or sigmoid colon was affected.

The diagnosis was confirmed in all cases by operation, X-ray, or, in one case, post-mortem examination.

Age and sex.—In Telling's collected series the main incidence fell in the age group 45–60, with a preponderance of males. In this series only one was below the age of 50 (she was 47) and 66% were over 60. There were 19 females and 5 males.

It is generally agreed that men are more commonly affected by diverticulitis than women and I can offer no suggestion as to why such a large percentage of the acute complications should occur in women.

History prior to acute attack.—12 of the patients had suffered from severe constipation for two or more years, 4 with occasional attacks of diarrhœa, and one with previous bleeding. One had had a resection done nineteen years before a similar attack. The other 12 had no previous bowel upset.

The acute attack.—Pain was the predominant symptom in 22 of the cases but in only one-third was it in the left iliac fossa. The usual site was the lower abdomen, both sides equally, and in a big majority of those where it was noted the pain was of a colicky nature. In one case the pain was entirely on the right side. Only one case had had a previous severe attack but a history of mild attacks was frequent.

Vomiting and nausea were other common presenting symptoms. Repeated vomiting of small quantities of fluid was noted in 6, severe obstructive vomiting in one, and marked nausea in 5 others.

Bleeding from the rectum was found in 3 cases and in 2 of them it was severe and the only symptom.

Constipation to fæces and flatus was present in 4 cases for 48 hours before admission.

Dysuria and frequency in one case was shown at operation to be due to an abscess from a gangrenous diverticulum adherent to the bladder.

The physical signs were out of keeping with the severe pain but *tenderness* was present to some extent in the left iliac fossa in 5, the hypogastrium in 3, the right iliac fossa in 2, and in 2 it was general throughout the abdomen. In 3 cases there was tenderness on rectal examination.

Rigidity was found in only 4 cases (in 2 in the right iliac fossa).

Distension, in varying degree, was seen in 8 cases. In one of these it was severe (a case of small bowel obstruction). In three it was associated with signs of peritonitis.

The classical *tender mass* was felt in only 3 cases (one was to the right of the umbilicus) although Telling gives the incidence as 30%.

TABLE I

Initial diagnosis	Number	Treatment	Result
Diverticulitis	14	Conservative	Recovery 14
Appendicits with peritonitis	6	Drainage 5 Paul's 1	Recovery 6
Band obstruction of small intestine	1	Separation from sigmoid	Recovery
Acute pancreatitis	1	Conservative	Death
Carcinoma of rectum	2	Conservative	Recovery 2

Diagnosis and treatment (*see* Table I).—These may be considered together because it is when the diagnosis is in doubt and when there are signs of peritonitis or acute obstruction that operative treatment is necessary.

In 14 cases the provisional diagnosis was diverticulitis. This group includes the 3 cases with a palpable mass and 5 cases in which definite obstructive symptoms and distension were present. Under conservative treatment recovery was rapid. In 6 cases there were signs of peritonitis—in 2 it was generalized. In none of these was the correct cause diagnosed pre-operatively—5 were thought to be appendicitis with either a pelvic or general peritonitis. These cases were operated on. 2 of them had a fæcal peritonitis due to an obvious perforation of a diverticulum: in 1, with only a localized area of sigmoid involved, a Paul's operation was done; in the other the perforation was over-sewn with omentum and the pelvis drained. In 4 other cases, where there was no obvious perforation but a local peritonitis or pelvic abscess, drainage only was carried out. Chemotherapy and parenteral fluids were given post-operatively in most cases. All these patients recovered and when seen up to two years afterwards had had no further severe attacks.

One case of acute small bowel obstruction was found to be due to adhesion and kinking of a loop of terminal ileum which was fixed to an acutely inflamed peri-diverticular mass arising from the sigmoid. The adhesions were separated and her post-operative course was satisfactory.

The 2 cases of severe bleeding from the rectum were thought at first to be carcinomata but investigations and follow-up have shown this to be incorrect.

All cases were subsequently given a low residue diet and regular doses of liquid paraffin ordered. Late mild recurrences of symptoms were treated by Sulphasuxidine by mouth and small enemata. Under this regime even those patients presenting as a relatively severe obstruction remained free from symptoms of stenosis. I cannot, in the same period—1945 to 1949—find one example of stenosis due to diverticulitis requiring operative treatment.

There was one death in this series: the diagnosis was not made during life.

The patient, a woman of 59, was admitted with a four-hour history of collapse and severe upper abdominal pain. She had vomited at the onset. Seen on admission she looked ill with a greyish cyanosis; there was tenderness throughout the abdomen but no rigidity. Six hours later she felt better, the pain was gone and her general condition had improved. The initial diagnosis was acute pancreatitis but the blood amylase was found to be normal. Three days later she developed a painful tender swelling in the left flank. Her general condition rapidly deteriorated. Penicillin, sulphadiazine and parenteral fluids were given but she died two days later. Her temperature was normal throughout. At post-mortem a fibrino-purulent peritonitis and diverticulitis were found. The pancreas and other organs appeared normal for her age.

Discussion.—These few cases help to illustrate certain points:

(1) The complications of diverticulitis occur in old people—the average age of the cases operated on was 59—often very poor surgical risks and this diagnosis should be thought of in any patient over 50 years of age with an "appendicitis" which is not quite typical, especially when the pain is colicky and in the mid-line below the umbilicus.

(2) Rectal bleeding can be very severe.

(3) Operative treatment is necessary only when there are signs of a spreading peritonitis or in the rare cases of acute small bowel obstruction.

(4) The performance of a colostomy or cæcostomy is rarely necessary and should be avoided. Drainage, supplemented by chemotherapy, is all that is needed even when there are symptoms and signs of large bowel obstruction as occurred in 3 cases in this series. This obstruction is only temporary and due to superadded inflammation.

(5) Obstructive symptoms, except small bowel obstruction, without peritonitis, should be treated conservatively by rest, small oil enemata, fluids by mouth or parenterally, and chemotherapy.

I am indebted to the Physicians and Surgeons of the General Infirmary at Leeds for permission to examine their case records, and especially those Surgeons who have allowed me to treat many of the cases in this series.

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Section of Proctology

President—MICHAEL J. SMYTH, M.Ch.

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DISCUSSION ON THE TREATMENT OF ADVANCED CANCER OF THE RECTUM

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In discussing a subject so vast as the management of advanced carcinoma of the rectum, it is necessary to have clearly in mind what is meant by "advanced" carcinoma; whether it be advanced by virtue of widespread metastases, advanced through nodal involvement or advanced by involvement of contiguous structures. This contribution will be limited to carcinoma of the rectum involving contiguous structures, accepting this as an advanced condition regardless of how small the initial lesion may be. I shall deal in particular with carcinoma on the anterior wall of the rectum involving the base of the bladder, seminal vesicles, prostate, or terminal ureter in such a way as to render anything but palliative operation in this area impossible. Only those cases will be considered who have this involvement of these contiguous structures yet have no evidence whatever of remote spread, metastases, physical depletion or other evidence which would render them inoperable or even suspect. These latter have in the past been considered amenable only to palliative operations and the usual 100% local recurrence has been indeed testament to their irremovability. The area between the base of the bladder and the rectum is shown under low-power magnification in Fig. 1. It will at once be seen that to strip either from the other, in case of contiguous carcinoma, is impossible in a cancer-curative sense.



FIG. 1.—Low-power magnification of area between bladder and rectum. Normal anatomy, showing how impossible it would be to leave any margin of safety in the stripping of contiguous carcinoma.

Not infrequently one sees an operable carcinoma of the upper rectum or lower sigmoid adherent to some one neighbouring viscus—whether a loop of small bowel, fundus of the bladder or even the abdominal wall. One frequently sees surgeons separating these from such contiguous structures and proceeding to radical resection. I believe this to be wrong. In my opinion it is very difficult to assuage the pangs of conscience by assuming that such adhesive mechanisms are perhaps largely inflammatory. If extirpative surgery is to be complete, then these structures should not be separated from the original carcinoma but should be resected with their contiguity undisturbed—whether it be the loop of small bowel, the fundus of the bladder, the uterus, or the abdominal wall musculature. Surely only by observance of such a doctrine can one hope to overcome the incidence of local recurrence so common in the past in resections of the left-sided colon and rectum (Fig. 1).

Cancer of the stomach, for instance, may be compared with cancer of the rectum, in order to contrast the hopelessness of the one with the hopefulness of the other. One must agree

that by comparison cancer of the rectum is usually of lower grade, slower growth, later extension, locally invasive and frequently supervening upon some benign growth. Size means nothing: a very large carcinoma may defeat itself by the very exuberance of its own growth; while the smaller ulcerative, penetrating type may be minute by comparison, yet of higher grade and more fearful portent. Table I shows five-year survivals of both cancer of the stomach and cancer of the rectum over the last twenty years. It shows with great clarity the warm hopefulness of the one and the cold hopelessness of the other. This tremendous difference in outlook merely emphasizes what I believe to be an accepted fact: that the modern partial removal of a stomach, the site of carcinoma, does not fulfil the criteria of adequacy acceptable for cancer removal to-day.

TABLE I.—FIVE-YEAR SURVIVALS

Gastric carcinoma	$\frac{356}{13}$ (3·6%)	Carcinoma of rectum	$\frac{356}{192}$ (53%)

I advocate complete extirpation of all contiguous structures to which an anterior wall rectal carcinoma may be attached, providing that it is possible, and only in those cases in whom there are no remote stigmata of carcinomatous spread and in whom all clinical forms of investigation such as chest plates, liver investigation, &c., are otherwise negative. It is not part of the purpose of this paper to advocate heroic massive resections of inoperable carcinoma with metastases in the hope of increasing the degree of palliation, but only in those cases where there is every hope of a permanent cure if the whole of the locally invaded area can be removed.

This presentation is based upon 9 such cases in which I have been able completely to remove the carcinoma locally invasive into the base of the bladder, prostate or vesicle and where there was no discernible evidence of remote involvement. In view of the splendid support which surgery nowadays receives from blood banks, plasma banks, improved anæsthesia and antibiotics, one can approach such major procedures with greater confidence than has been possible in the past. The freeing of the bowel from the incubus of hostile bacteria has itself been a gigantic stride and the emphasis of pre-operative preparation of such cases bears little resemblance to the casual haste of yester year and justifies extensive one-stage procedures.

The problem of vascular control in such pelvic eviscerations in the male is much simplified if the arterial supply is attacked as a primary venture at its source. The inferior mesenteric artery with its terminal superior hæmorrhoidal branch is first ligated and then it is my custom to place a ligature around each internal iliac artery just below the origin of the gluteal branch. This controls almost all of the arterial bleeding which one encounters in such eviscerations. While it does not control venous bleeding in any way, I have found that the venous bleeding is of little consequence if the arterial supply has been previously ligated. An X-ray picture of an injected internal iliac artery to show its distribution to the visceral elements of the pelvis is here shown. It clearly emphasizes the vast network of arterial anastomoses which occur around the base of the bladder and front of the rectum. Such a ligature is not difficult and is a time-saving device of great value (Fig. 2).

I remove all the pelvic viscera intact, including the full lymphatic and venous drainage area of the rectum, the levatores ani right out to their source, the lateral ligaments of the rectum and all of the veins, nodes and ischiorectal fat pads in one complete block.

In the first series of six, I was at some pains to create a new floor for the abdominal viscera by the elevation of flaps from the sides as one does in routine abdominoperineal resections. In one or two instances, these flaps failed to hold and the speed with which the endothelialization of the bared walls of the pelvis developed amazed me—to the extent that I now no longer attempt to form a floor if it presents difficulties. I allow the small bowel to drop down where it may, knowing that full endothelialization of the pelvic walls will occur very rapidly. In a case of ordinary abdomino-perineal resection which subsequently required reopening for another cause and in which the floor had given way, the small bowel was down in the pelvis, a new endothelium had formed and there were scarcely any adhesions of consequence present at all. I believe that an experience such as this justifies the elimination of the floor which may become a difficult thing to create when the whole of the pelvic viscera have been removed.

Bilateral ureteral transplant into the bowel in the presence of colostomy produces a chain of miseries all its own, as the vast array of gadgets, plugs, tampons, trick colostomies and skin-grafted loop protrusions is surely testament. Having in my first few cases faced such difficulties, I decided to try and ameliorate the lot of those who must endure such a catastrophe as the price of continued existence. So, having transplanted the ureters into the cæcum for other reasons many times hitherto, I deliberately transplanted both ureters into the cæcum in one of these cases in the hope that the transport of the urine through the



FIG. 2.—Injected internal iliac arteries showing vascularization of pelvic structures. On the right side some reflux of injected material is shown in the external iliac and femoral arteries.

large bowel might result in reabsorption of much of its watery content. I did this in the belief that the colon would not absorb the deleterious products of urinary excretion to any degree. I have made a few interesting observations upon the electrolyte balance and fluid contents of bowels into which urine has been proximally transported. My object in using the cæcum is that it is nature's cesspool; it is a less active part of the bowel and water absorption takes place readily from the colon between the cæcum and the point of exit of the colostomy. From such measurements as I have been able to devise, it is my belief that there is approximately a 30% less fluid efflux from such a colostomy than if the ureters are transplanted into the bowel immediately above the area which is exteriorized as a colostomy. Regardless of how much improvement there may be, however, it is definitely my opinion that no colostomy is leak proof if the bowel has to put up with a bilateral ureteral transplant, no matter into what area of bowel they may have been implanted. Some form of control is mandatory. In my own experience I have found that, while nothing is perfect, the one most frequently liked by patients and the one most often used, is the simple Foley bag type of urinary retention catheter which can be inflated by the patient to his own requirements or his own sense of comfort. It is easily handled, easily replaced, not too expensive and, on the whole, remarkably efficient.

At times ill-considered statements have been made that a right-sided ureteral transplant is incompatible with life. I am at present convinced and have been for many years that this is not so. I have had one child survive for twenty-one years with all the urine going into the cæcum. I have repeatedly shown by radiological investigation that, when the ureters are implanted into the sigmoid in other types of cases, intravenous urogram dye excreted into the bowel can be seen to sluice around all the way into the cæcum in any event, so that even a left-sided implant is no proof or safeguard against right-sided absorptive procedures. I have a different explanation for the frequent attacks of an acidotic state which some of these ureteral transplant cases develop, whether they be right- or left-sided. The sense of weakness, the sodium chloride resorption from the bowel, the low CO_2 combining power, all are to be found in those cases in which there is a greater or lesser degree of incompetency of the ileo-cæcal valve. It is in these cases, where such urinary contents are permitted to sluice back into the small bowel, that such electrolytic disturbance is most in evidence. While it is by no means an explanation of all of the phenomena, the cases in whom urine does go back into the small bowel have much more severe and frequent attacks of such

acidotic states than do the others. It is my routine procedure in all such cases where urine is transported into the bowel to put them on a low chloride, low fluid intake, and to give them adequate quantities of sodium bicarbonate daily or as required. By such alkalinization and such dietary limitation of chlorides and fluids, with Foley bag local control, life can proceed on a very comfortable and equitable basis. I have made repeated investigations of the level of blood non-protein nitrogens in these cases. I have practically perfused the large bowel, in ordinary cases where a cæcostomy is present, with the products of urinary excretion: urea, creatinine, &c., and failed to find any appreciable absorption of these substances from the large bowel regardless of what quantities or concentrations the bowel was so perfused. Careful investigations of CO_2 combining power and sodium chloride retention or resorption have shown the two to run fairly closely parallel. It is my belief that an intelligent understanding of the ætiological basis of these acidotic states can only lead to a regimen which adequately controls or prevents it.

Low Chloride High Alkali Diet.

The following foods may be used: Apple butter, berries, cabbage, chestnut, citrus fruit (except limes), corn (sweet), cucumber (fresh), currant (fresh), egg plant, figs (fresh), fruit juices (including prune juice), goat milk, grapes, jellies, maple syrup, mushrooms, onions, orchard fruit, parsnips, peppers (green), pomegranates, string beans, tapioca cream, water-melon, cornstarch, squash, tomato, tea, coffee, sugar, vinegar.

Foods to be avoided: Salt and all salt substitutes. Meat, fowl, fish in all forms, cheese, eggs, cream and milk except goat milk. Bread and all other cereal foods. Condiment and pickles.

SUGGESTED MENU—

Breakfast: ½ grapefruit, ½ cup boiled unsalted rice, 1 cup goat milk, sugar as desired, coffee.
Lunch: Fruit or vegetable salad, tapioca cream (using goat milk), tea and sugar.
Dinner: Tomato juice, vegetable plate with cabbage, sweet corn, string beans, baked apple, goat milk, tea with sugar as desired.

Questions have been raised as to the degree of ascending infection which occurs in the transplant of the ureter into the cæcum with its liquid contents, as opposed to the left-sided transplant. I believe that an ascending infection of a kidney only occurs if the ureter is partially obstructed; that if any form of clamp is used on the end of a ureter a pin-point opening of that ureter through a subsequent cicatricial contracture is almost inevitable and, that this fine jet requiring some force for its expulsion, occasions a certain amount of ureteral dilatation and minimal hydronephrosis and is the proving ground where ascending infection may develop. In my opinion, if the ureter is not too extensively mobilized, so that its peristalsis is not seriously interfered with, if its tip is shown at the time of implant to be well vascularized and pink, and if nothing is tied into the ureter which would assist in its drainage temporarily but eventually lead to a narrowing of its orifice, the degree to which urinary ascending infection occurs is wholly minimal. In these days of aureomycin, particularly of intravenous aureomycin, we have had almost complete control of all our cases of ureteral transplant from the standpoint of ascending infections ever since its use has been instituted. Without hesitation we place all such cases on intravenous aureomycin, and supporting oral aureomycin from the day the transplants are made into previously sterilized bowel. It is my belief that the infected transplanted ureter is an obstructed ureter and I believe the mucosa to mucosa transplant which enjoys such favour at this time is more likely to lead to such ultimate pin-point opening than is the freely clipped pendulous implant where no such suture interference with the terminal ureter is permitted.

It is highly probable that the use of defunctionalized bowel loops may entirely supplant the implant of ureters into fæces-containing bowel and that the patient may ultimately have to put up with two exteriorizations: one for the urine and one for fæces, as the price of safety.

CONCLUSION

This presentation is made as a plea for the expansion of the scope of extirpative surgery of the rectum when small lesions, without remote spread, are invading by contiguity structures which can be removed and without which life need not be too formidable.

It is presented (1) as a record of my own method of transporting the ureters into the cæcum rather than into the sigmoid and my reasons for so doing. (2) In order to report the primary ligature of all arterial supply to the part in order to minimize the hæmorrhage incident to such extensive removal. (3) To record my belief in the fact that the floor of the pelvis need not be reperitonealized: that the contact of the bowel with these raw surfaces will lead to its early endothelialization in much the same way as a large incisional hernia will endothelialize its walls. (4) It is presented in the belief that local infiltration of rectal carcinomata is as a rule of sufficiently low grade to warrant the most widespread removals in the interest of cure rather than palliation. It is my hope that some suggestions contained herein may lead others to develop perhaps a better operation which may in turn bring cure or amelioration of the sufferings of a group of people which has been considered amenable only to palliative surgery.

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Early in the twentieth century Ernest Miles published his concept, "A Method of Performing Abdomino-perineal Excision for Carcinoma of the Rectum and Terminal Portion of the Pelvic Colon". He was much concerned about residual disease found within the pelvis, after the commonly practised perineal excision of rectal cancer. From his observation and diligent examination of involved areas of lymphatic spread, a better reatment for cancer of the rectum has evolved.

In the years which have passed there have been many deviations from the Miles concept. Some methods have contributed advances, others have been of negative value. Unfortunately, many limited resections are being perpetrated in the name of the Miles method. These procedures are particularly inadequate in removal of tissue about the inferior mesenteric vessels, the pelvic peritoneum, the levatores ani with their associated fascial structures, and the ischiorectal space contents. There is a constant sentiment among surgeons to preserve the anal sphincter mechanism at the expense of an inadequate resection. With all these thoughts in mind, and in view of reported statistics, I think we can state that the treatment of cancer of the rectum and resultant overall cure rate has become static.

The Colon and Rectal Service of the Memorial Hospital reports a 52% five-year survival rate in 423 patients having abdominoperineal resection of the rectum for cancer. The operative mortality rate was 5·7%.

During a detailed post-operative follow-up of our patients and surgical re-exploration of those having residual disease, we have been impressed with certain findings. A review of 150 patients having residual rectal cancer after abdominoperineal resection, revealed that 50% had initial findings limited to structures within the pelvis. The remaining 50% showed metastases to the liver, lungs, brain, bony skeleton and subcutaneous areas. It was quite apparent that a more extensive initial effort must be made to remove the primary rectal cancer and its regional lymphatic drainage areas. In the female, residual disease was frequently found in the genital tract, especially the posterior vagina, ovaries, and, in a few cases, the uterus. In the male, a common site of residual disease is within the thin fascia posterior to the seminal vesicles and the posterior prostate gland. Cancer in this area soon extends to the bladder base. Dr. Lyon Appleby of Vancouver, B.C., has so ably demonstrated this idea in his work. These pelvic extensions may be by lymphatic spread or by direct invasion. In my experience involvement of the obturator and hypogastric lymph nodes by metastatic rectal cancer and spread to the inguinal areas is more common than is generally recognized. I find also that there is lymphatic spread to the lymph nodes adjacent to the greater pelvic vessels, the lower abdominal aorta and vena cava. To correlate these findings with their probable routes of spread, a study of Rouvière's "Anatomy of the Human Lymphatic System" has been most helpful.

To set up a programme for a more radical attack on rectal cancer, it was necessary to designate a clinical criterion as to the type of lesion which would be so treated. Therefore, in the initial series, all annular rectal cancers, those circumscribed but deeply ulcerated, and small mucosal lesions with evidence of submucosal induration were considered as advanced disease.

In such advanced disease, with lesions at the pelvic peritoneal reflexion or below, the Miles type of abdominoperineal resection of the rectum is employed with the following modifications. The inferior mesenteric artery is ligated at the aorta or just below the left colic artery. The aortic sympathetic plexus is interrupted at the level of the transverse portion of the duodenum and the plexus, with the underlying para-aortic lymph nodes, is stripped distally to the bifurcation of the aorta (Fig. 1). The dissection is continued to include the promontory, iliac, hypogastric and obturator lymph-node areas (Fig. 2). In the female, bilateral salpingo-oophorectomy, total hysterectomy, dissection of the broad ligament contents and excision of the proximal half of the vagina are done. When there is definite invasion of the mid-portion of the vaginal tube, complete removal of the vagina is advocated. I believe the incidence of residual disease in these areas and organs justifies this radical approach (Figs. 3 and 4).

In the male, in anterior, infiltrating or annular lesions at the level of the seminal vesicles or posterior prostate, both vasa deferentia are interrupted above the seminal vesicles, and the vesicles with the posterior one-half or two-thirds of the prostate are removed with the rectum (Fig. 5).

In previously hysterectomized patients and male patients with invasion of the base of the urinary bladder by apparently localized disease, proctocystectomy with removal of the pelvic viscera must be done. The ureters may be implanted into the remaining large bowel or into an isolated segment of the large bowel. Dissection of the pelvic lymph nodes and those accompanying the great vessels of the lower abdomen should be done as part of the initial procedure. Inguinal lymphadenopathy may be dissected at a later stage.

In a series of 25 patients having abdomino-pelvic lymph-node dissections, 24% had metastases in nodes other than the intermesenteric and pararectal node groups (Table I).

TABLE I.—ABDOMINO-PELVIC NODE DISSECTION WITH MULTIPLE ORGAN RESECTIONS

Patient	Age	Tumour site from anal margin	Operative specimen	Abdomino-pelvic nodes	Condition and survival
N. T.	32	8 cm. Anterior wall	Adenoca. Gr. II Dukes C	Negative	N.E.D. 2 yr. 5 mo.
A. B.	55	6 cm. Ann. inv. vag. wall	Adenoca. Gr. II Dukes B	Negative	N.E.D. 2 yr. 3 mo.
A. B.	50	5 cm. Ant. inv. vag. bilat. groin	Squamous ca. Grade III	Bilat. groin Rt. C. iliac	L.W.D. 2 yr. 3 mo.
R. M.	32	12 cm. Ant. extrin. inv. vag. and cx.	Adenoca. Gr. IV	Negative	L.W.D. 1 yr. 5 mo.
F. T.	67	6 cm. Ant. inv. seminal vesicles	Adenoca. Gr. II Dukes C	Pos. R. and L. obturator Pos. R.C. iliac	N.E.D. 1 yr. 5 mo.
T. E.	36	17·5 cm. Annular	Adenoca. Gr. II Dukes C	Pos. R. para-aortic Pos. R.C. iliac	N.E.D. 1 yr. 3 mo.
T. M.	42	15 cm. L. lateral wall	Adenoca. Gr. II Dukes A	Negative	N.E.D. 1 yr. 3 mo.
B. P.	43	7 cm. Ant. inv. seminal vesicles	Adenoca. Gr. III Dukes B	Negative	N.E.D. 1 yr. 2 mo.
P. T.	57	8 cm. R. lat. met. both ovaries	Adenoca. Gr. III Dukes C	Negative	N.E.D. 1 yr. 1 mo.
S. H.	51	20 cm. Annular	Adenoca. Gr. III Dukes C	Negative	N.E.D. 1 year
J. R.	56	9 cm. Posterior inv. coccyx	Adenoca. Gr. II Dukes B	Negative	N.E.D. 10 months
G. S.	41	7 cm. Anterior	Adenoca. Gr. II Dukes B	Negative	L.W.D. 9 months
J. C.	40	15 cm. Annular	Adenoca. Gr. III Dukes B	Negative	N.E.D. 8 months
M. M.	63	5 cm. Annular	Adenoca. Gr. II Dukes C	Pos. prom. and Rt. and Lt. hypogastric	N.E.D. 8 months
A. M.	56	5 cm. Anterior	Adenoca. Gr. II Dukes A	Negative	N.E.D. 8 months
J. G.	65	7 cm. Anterior	Adenoca. Gr. III Dukes B	Negative	N.E.D. 7 months
W. H.	58	15 cm. Annular	Adenoca. Gr. III Dukes C with vein invasion	Negative	Died disease 7 months
E. G.	42	5 cm. Annular	Adenoca. Gr. III Dukes C	Promontory	N.E.D. 7 months
O. A.	59	3 cm. L. lateral	Adenoca. Gr. III Dukes B	Negative	N.E.D. 6 months
H. N.	67	Anal canal. Inv. vagina	Squamous carcinoma Grade II	Negative	N.E.D. 6 months
J. McM.	35	5 cm. L. lateral	Colloid carcinoma Dukes B	Negative	N.E.D. 6 months
P. McC.	52	5 cm. L. lateral	Adenoca. Gr. II Dukes C	Negative	N.E.D. 6 months
M. E. F.	58	10 cm. Annular inv. lower uterine segment	Colloid carcinoma Dukes C	Negative	N.E.D. 5 months
G. F.	44	6 cm. Anterior	Colloid carcinoma Dukes B	Negative	N.E.D. 2 months
L. N.	54	6 cm. Annular	Adenoca. Gr. III Dukes C	Pos. R. hypogastric and obturator	N.E.D. 2 months

Positive abdomino-pelvic nodes .. 24%

D—Deceased. N.E.D.—No evidence of disease. L.W.D.—Living with disease.

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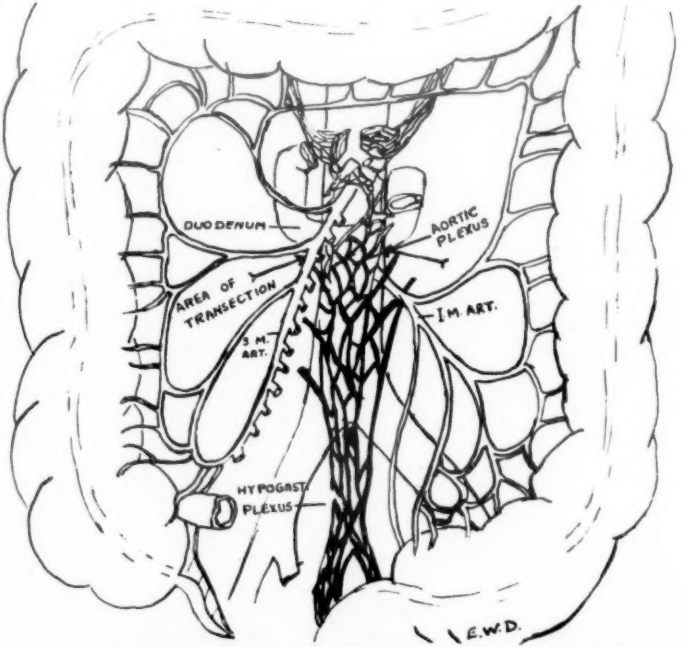


FIG. 1.—Autonomic nervous system. Fibres of the aortic plexus are intimately associated with the aorta and vena cava. These fibres must be elevated to expose the para-aortic lymph nodes.

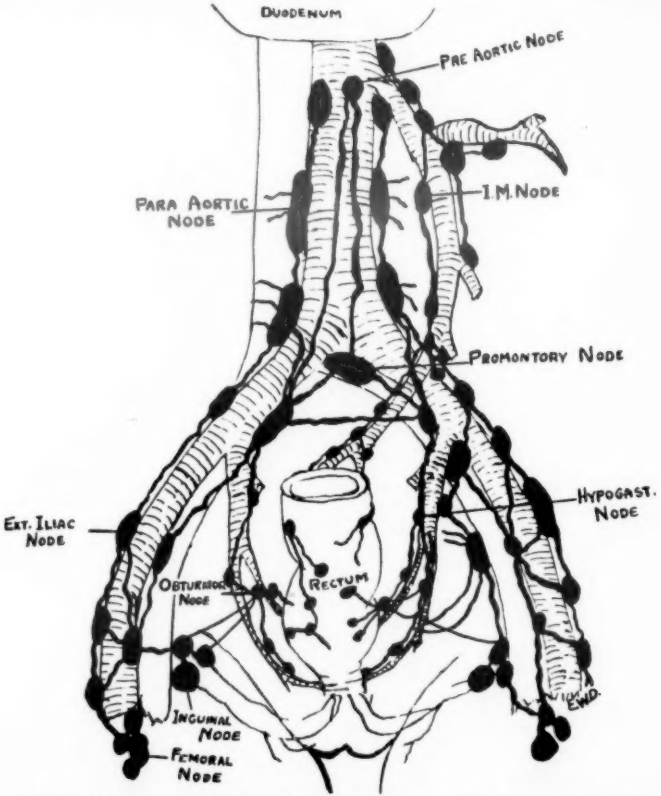


FIG. 2.—Lower abdominal pelvic lymph nodes. The lymph-node chains illustrated represent those removed at resection except for the external inguinal and femoral lymph nodes.

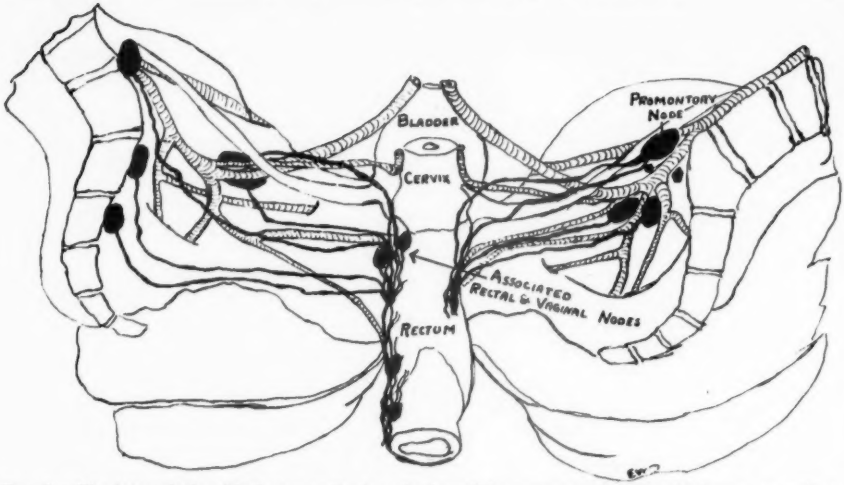


Fig. 3.—The interrelationship between the lymphatics of the rectum and vagina is shown, as well as drainage to the hypogastric and promontory lymph nodes. (After Rouvière.)

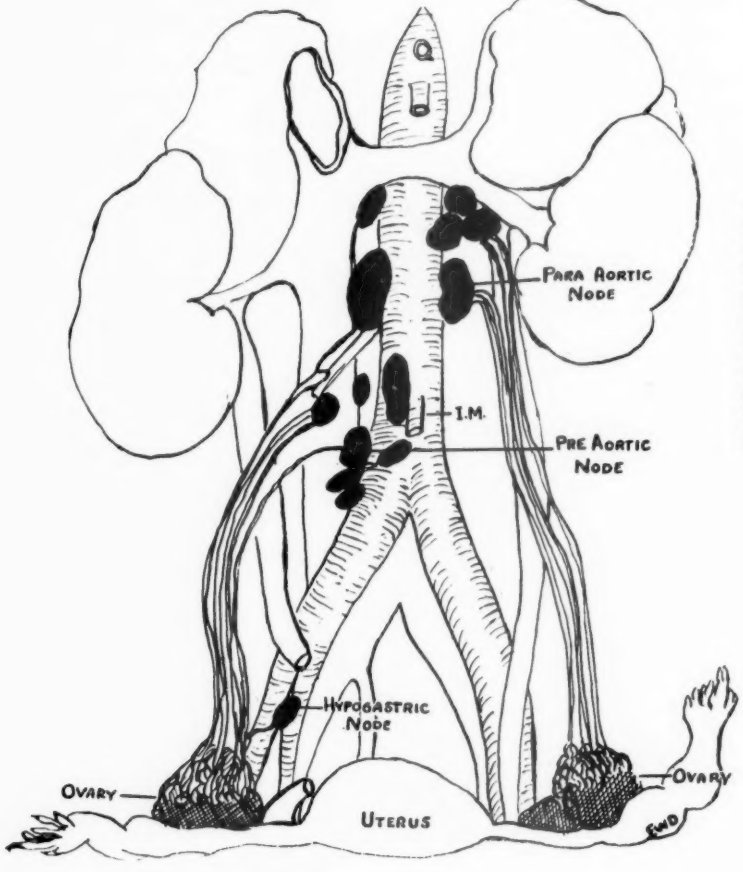


Fig. 4.—A route of possible metastatic spread of cancer of the rectum through the hypogastric lymph node to the ovary and para-aortic lymph nodes is illustrated. (After Rouvière.)

Organs adherent to a cancer of the terminal portion of the pelvic colon and rectum should be resected. Radical removal of pelvic organs within the same lymphatic drainage area must be considered at the initial surgical procedure (Table II).

TABLE II.—RESECTION OF RECTUM, PELVIC COLON AND ADJACENT ORGANS

Patient	Age	Tumour site from anal margin	Operative procedure	Operative specimen	Condition and survival
M. C.	54	7·5 cm.	Abdominoperineal '43	Adenoca. Gr. II	
		Metastasis to uterus	Abdominoperineal of uterus and vagina '48	Metastatic adenoca. Gr. II	L.W.D. 7 years
A. S.	42	20 cm. involving bladder	Hartmann, partial resection bladder '45	Colloid carcinoma Gr. I—Dukes B	
			End-to-end anastomosis '48		N.E.D. 5 yr. 3 mo.
R. J.	53	17·5 cm. adher. lower uterine segment	Hartmann, panhysterectomy '46	Adenoca. Gr. III Dukes C	
			End-to-end anastomosis '49		
		Metastases to rt. femoral nodes	Rt. hip disarticulation '49	Metastases to rt. femoral nodes	L.W.D. 4 years
E. P.	67	9 cm. invading uterus and ileum	Abdominoperineal, panhysterectomy, resection of ileum '46	Adenoca. Gr. III Dukes C	N.E.D. 3 yr. 5 mo.
A. J.	45	10 cm. invading uterus and ileum	Abdominoperineal, panhysterectomy, resection of ileum '48	Colloid carcinoma Dukes B	N.E.D. 2 years
C. S.	50	4 cm. invading cul-de-sac	Abdominoperineal, panhysterectomy, vaginectomy '48	Colloid carcinoma Dukes C	N.E.D. 2 years
M. H.	52	13 cm.	Segmental resection with end-to-end anastomosis '47	Colloid carcinoma Dukes C	
		Metastasis to rt. ovary	Rt. oophorectomy '49	Metastatic ca.	D. disease 2 years
F. Z.	64	5 cm. invading prostate and bladder	Proctocystectomy, transplantation of ureters to isolated desc. colon segment '48	Adenoca. Gr. II Dukes B	N.E.D. 2 yr. 1 mo.
M. K.	40		Lt. Salpingo-oophorectomy '45	Papillary adenoca. ovary	
		12 cm.	Abdominoperineal, rt. salpingo-oophorectomy '46	Colloid ca. Gr. I, papillary adenoca. ovary	D. disease 1½ years
M. LeG.	51	7·5 cm. invading recto - vaginal septum	Abdominoperineal, panhysterectomy, vaginectomy '47	Adenoca. Gr. II Dukes C	Died cerebral accident 9 months
M. B.	57	8 cm. invading lower uterine segment	Abdominoperineal, panhysterectomy resection proximal vagina '48	Adenoca. Gr. II Dukes C	D. disease vaginal stump 9 months
M. C.	62	8 cm. invading cervical stump with metastasis to rt. ovary	Abdominoperineal, bilat. salpingo-oophorectomy, excision cervix and proximal vagina '49	Adenoca. Gr. II Dukes C	N.E.D. 6 months

Deeply ulcerated posterior lesions invading the sacrum have been treated by limited resection of the sacrum. Our results have been uniformly poor. However, some recent work by Drs. Coley and Higinbotham of the Memorial Hospital in the resection of the sacrum for sacral chordoma is encouraging. They have removed the distal three segments of the sacrum without apparent disability except for temporary rectal and bladder dysfunction. Hemipelvectomy should be considered when the lateral bony pelvis is involved.

Technically, radical resection of the rectum and dissection of adjacent lymphatic-bearing structures is more difficult in the male because of the smaller pelvic cavity and bleeding from the prostatovesical venous plexus. Obesity is a handicap in either sex.

There has been increased post-operative morbidity in these radical resections and node dissections for rectal cancer. This is particularly manifest in the urinary tract as bladder dysfunction, infection and azotæmia. There have been no operative deaths in this series. Strict post-operative supervision is mandatory.

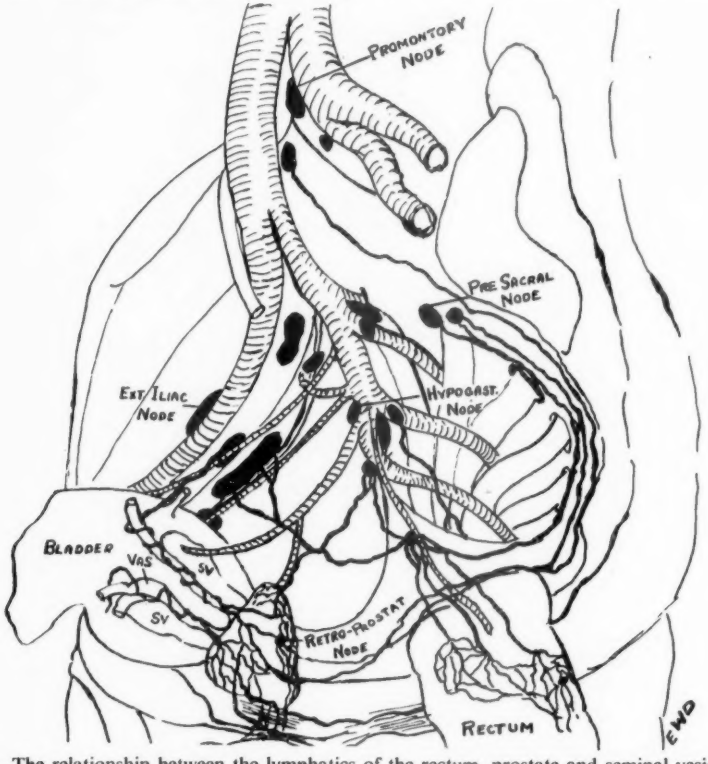


FIG. 5.—The relationship between the lymphatics of the rectum, prostate and seminal vesicles and their common drainage areas. (After Rouvière.)

A definite follow-up examination of every post-operative patient must be instituted. This should be at two to three month intervals for the first three years and at four to six month intervals for the remainder of the patient's life. Dr. Owen Wangensteen has recently stated that exploratory laparotomy to determine possible residual rectal and colon cancer should be advocated approximately six months after the initial surgical procedure. This criterion for re-exploration is supported by the results of an experimental series in his clinic. 20 patients having node-positive findings at the initial operation were re-explored, and 75% were found to have residual disease. Certainly, when there is evidence of any possible residual disease, every effort should be made to determine its presence or extent and immediate treatment instituted. In recent years many gratifying results have been seen in re-operating these patients. When feasible, patients with solitary lung metastasis from rectal cancer should have thoracotomy and resection.

Non-resectable residual cancer within the lower abdomen and pelvis should have an attempt at palliation by high voltage or supervoltage X-ray therapy. This therapy should be accurately outlined after consultation between the surgeon and X-ray therapist at the patient's bedside. The response of residual rectal cancer to X-ray therapy cannot be predetermined by the differentiation of the tumour type and this criterion should not be used to withhold such treatment.

The use of X-ray to control infection and intrathecal alcohol as sensory nerve block have been, in our experience, the most effective palliative agents.

With our present physical methods, patients afflicted with rectal cancer might be given a greater extension of life, though I realize that a decade must elapse before results can assess the value of this type of surgery.

SUMMARY

(1) All annular rectal cancers, those circumscribed but deeply ulcerated, and small mucosal lesions with evidence of submucosal induration, are considered as advanced disease.

(2) The initial surgical attack on rectal cancer must widely remove the primary cancer, with any adherent organ and the regional lymph node-bearing tissues.

(3) A concept of the extent of lymphatic spread in rectal cancer to adjacent organs and abdominopelvic lymph nodes is suggested.

(4) Metastatic cancer has been demonstrated in lymph nodes outside the intermesenteric and pararectal groups in 24% of a clinically selected series.

(5) There has been increased morbidity in these extensive surgical procedures for removal of cancer of the rectum and terminal portion of the pelvic colon. Complications involve the urinary tract primarily.

(6) Strict post-operative follow-up and re-exploration for residual disease is advocated.

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Dr. James W. Morgan and Dr. John B. de C. M. Saunders, *San Francisco*:
Preservation of Genito-Urinary Function in Rectal Resection

The high frequency of genito-urinary difficulties after radical resection of the rectum for malignant disease is well known. Many writers have stated that the incidence of vesical dysfunction following resection is from 50% to 100%. These figures simply testify to the

fact that the radical operation for cancer of the rectum is *usually* followed by bladder complications. Cuthbert Dukes stated that "catheterization is always necessary after operation, and whether the bladder is drained by a restrained or indwelling catheter, or by repeated passage of catheters, the hazard is incurred that a urethritis, cystitis, or even a pyelonephritis will develop as a sequel to the surgical treatment".

Measures for the control of these factors have been instituted by most surgeons. Preoperative attention to the urinary tract, the maintenance of rigid precautions in catheterization, and meticulous care in the details of operative procedure have been emphasized, but too little attention has been paid to the role of the bladder nerve supply, nor have proper measures been suggested for its preservation.

It is our opinion that the damage to the pelvic parasympathetic outflow is primarily responsible for the majority of the genito-urinary complications following rectal resection. The preservation of these nerves enables the surgeon to discard the catheter post-operatively in the majority of cases and, furthermore, preserves sexual function in the male and reduces shock in the operative procedure. Conservation of the parasympathetic outflow does not, in our experience, render resection less radical nor does it increase the hazard of recurrence.

The nerve supply to the genito-urinary apparatus is derived from three sources: somatic, sympathetic and parasympathetic. The somatic element from the pudendal nerves supplying the voluntary muscles we may dismiss as relatively unimportant to the topic under consideration except to observe that occasional injury to them has been reported with attendant incontinence, owing to the paresis of the urethral sphincter. The sympathetic pathway is well known in view of the great interest in the hypogastric plexus and presacral nerve. The relations of the *parasympathetic* pathways are of much greater importance to the subject under discussion. Derived from S.2, 3, and 4, these nerves go to form a massive plexus on either side. Quite unlike the descriptions usually found in textbooks, these nerves sweep forward on the inside of the posterior lateral wall to surround the bladder neck.

The parasympathetic plexus is ensheathed in a distinct layer or condensation of pelvic connective tissue which lies anterior to the presacral fascia and lateral to or outside the fascia propria of the rectum. Division of the parasympathetic outflow results in inability to empty the bladder, to loss of muscular tone and to paralysis of the mechanism controlling the erectile tissues of the genitalia. The injury may be unilateral or bilateral. Animal experimentation and clinical experience have convinced us that afferent impulses from the bladder, so necessary to the emptying reflex, are carried exclusively by way of this system. The urinary dysfunction following excision is commonly due to destruction of this parasympathetic pathway and this destruction may be partial or complete. It is usually during the perineal stage or posterior resection that the nerves are torn. It is therefore important to recognize the plane in which these nerves lie and the technique of their isolation. It is necessary to remove the coccyx and once this has been excised, the operator encounters a thick sheath of fascia which is made up of the periosteum and the blended presacral layer of endopelvic fascia. A vertical mid-line incision through this sheath of fascia discloses a second and separate layer which is often, but incorrectly, regarded as the fascia propria of the rectum. Development of the plane between these two layers of fascia will only result in disruption of the nerves near the sacral foramina with attendant paralysis of the bladder to a greater or less degree.

If the second layer is carefully incised in a vertical direction, a plane of cleavage will be encountered which can be opened and extended laterally and forward with the aid of the operator's finger. Anterior to this space is the fascia of the rectum and the rectum itself. Development of the proper cleavage plane enables the surgeon to push the parasympathetic trunks out of harm's way and only the nerves which pass to the rectum are divided.

We submit an analysis of 269 operations performed in the past eleven years. The great majority, 184, were one-stage Miles' abdominoperineal excisions. The remaining 85 were either two-stage "Mummery" operations or posterior excisions somewhat similar to those performed by Jerome Lynch. The two latter procedures were used for patients who were poor operative risks and whose neoplasms were low down. Many of our patients had extensive involvement.

Of these patients, only 21 (7·8%) needed catheterization for more than seven days and of these, 15 had metastases to the vesiculæ seminales or other pelvic organs so that complete extirpation was not carried out. 155 patients (57·6%) required no post-operative catheterization at all. It is to be emphasized that following the teachings of Miles, a catheter was never used during the operation, although every patient was catheterized prior to surgery. In our opinion an indwelling catheter is not necessary for proper dissection and only invites trouble.

It is difficult to evaluate the cases as to absence of shock but we feel that if the parasympathetic trunks are identified, retracted and not torn there is less operative shock.

172 (64%) of our patients were men of from 28 to 91 years of age. Obviously the

preservation of sexual function following operation is important, if only on a psychological basis. We were unable to obtain exact data in this regard but the great majority of the younger men have been questioned and if they told us the truth, they were unaffected by the operation and there was no loss of sexual power.

It is our opinion that it is the damage to the pelvic parasympathetic outflow which is primarily responsible for the majority of the genito-urinary complications following rectal resection.

Dr. I. G. Williams, *St. Bartholomew's Hospital, London*: *The Use of Radiotherapy in the Treatment and Management of Inoperable Carcinoma of the Rectum.*

This contribution deals with adenocarcinoma, and squamous carcinoma of the anal canal has not been included. Radium therapy has extremely limited application, whilst the effects and results of 200 kV. deep X-ray therapy were so universally poor that their use has been abandoned, except perhaps in the treatment of the few patients with localized, superficial, most often perineal, post-operative recurrences. The difficulties with 200 kV. therapy are due to the fact that the difference in radiosensitivity of an adenocarcinoma, and the normal rectal mucosa is so slight that the reactions produced, severe, painful and prolonged in all cases, do not justify the very occasional benefit which may be obtained. Rays generated at higher voltages are essential, and our cases have been treated at one million volts.

Advantages.—(1) There is a greater depth dose, so that in proportion to the dosage on skin a greater percentage reaches a depth. Fewer fields have to be used in order to achieve a desired tumour dose, and thus less normal tissue is irradiated. Because of this the treatment is easier, more accurate and so more efficient.

(2) We do not consider that there is any proof of a greater differential biological action due to the shorter wavelength of the ray used.

The scope of radiotherapy is naturally greater than surgery for the inoperable case, for one can still attempt to eradicate the disease from the patient so long as it remains confined to a localized volume of tissue. Two questions thus arise: Can advanced but localized disease be eradicated? What degree of palliation can be expected in those that are not "cured"?

Before coming to these I would like to discuss two other aspects of radiotherapy: the severity of the treatment, and the risks and dangers involved.

The severity of treatment.—The treatment is a severe ordeal for the patient. It has to be carefully planned and carried out. The tumour-bearing region must be defined in a section of the body so that skin fields may be chosen, and the maximum radiation given to the tumour, with a minimum to the surrounding normal structures. Almost all patients experience some symptoms of the so-called general reaction, with lassitude, nausea and even vomiting and this may last the whole four to six weeks of treatment. After the second week local reactions in organs lying in the path of the beam add to the discomfort of the patient, radiation cystitis, colitis and vulvitis. The degree and frequency, of course, vary but most patients exhibit them to some extent. Blood changes occur, especially leucopenia and towards the end of treatment, skin reactions set in to add to the discomfort of the patient.

The hazards of radiation therapy.—These are due to the late changes.

Reactions occurring during treatment can be managed, alleviated and dealt with, but the late ill-effects are serious.

Fibrosis: (1) Pelvic fibrosis (post-irradiation). This is manifest by pain due to involvement of the sacral and lumbar nerves. It may cripple a patient, a patient who otherwise shows no evidence of growth. It occurred in 6 of our cases, although one cannot of course be certain that growth is entirely absent in these cases.

(2) An anal stricture or stricture of the rectum at the site of the growth. This is due to two factors: (*a*) Destruction of the tissues of the bowel wall and its replacement by fibrous tissue. (*b*) Radiation effects on the blood vessels causing a progressive endarteritis obliterans and resulting in further increase in the fibrous tissue in the bowel wall: a dense rigid stricture forms in which no mucosa can be recognized. The stricture has three complications.

(i) Chronic intestinal obstruction necessitating colostomy. This had to be done in two of our survivors—2 cases who had no clinical evidence of carcinoma three years after radiotherapy.

(ii) A chronic ulcer (necrosis) may develop. This mimics carcinoma very closely in its symptomatology and sigmoidoscopic appearance. One of our patients developed such an ulcer on the bowel wall twelve months after therapy.

(iii) Pelvic fibrosis may involve the ureters and cause a hydronephrosis.

Fistula due to radiation necrosis of normal tissue or tumour. The commonest is, of course, rectovaginal and this occurred in 12 of our cases.

Necrosis: Chronic radiation necrosis. This occurred in 6 cases. Some of these are slight, an area of dry chronic ulceration on perineal skin showing the changes of chronic radio-

dermatitis. Some were serious, with huge ulceration involving skin, sacrum, coccyx and perineal tissues. In the treatment of cancer, when the object is radical removal of the growth, radiation necrosis is a risk which has to be faced. The aim is, of course, to avoid it, for the patient is in a worse condition than if left alone to die from the cancer. It was commoner in earlier days when less was known about the agent we use, and its proper prescription. But in spite of the most careful planning and execution it still occasionally occurs, for patients vary, tissues vary, blood vessels vary. Radiation necrosis affects the surface tissues, which receive the highest dose, and the wound is plain for all the world to see, a horrible, painful, foul ulceration, resulting in chronic invalidism, existence and suffering prolonged. Its incidence is much less in recent years but we must be prepared for it when it does develop for it is a hazard which has to be faced the same as the morbidity and mortality of surgical treatment.

RESULTS

Total—237 cases

	Treated	Alive	Lived (three years or over)
Stage 1. Confined to mucosa	6	3	1
Stage 2. Involves whole bowel wall or local pelvic mets.	21	2	7
Stage 3. Fixed to pelvic tissues	120	11	27
Stage 4. Distant metastases	20	3	3
	167	19	38
Recurrent	70	11	19

Five-year survival—Treated up to 1944: 127. Alive and well: 8

Survival.—It will be appreciated that 140/167 or 84% were too advanced for any form of surgery, and even the early cases were unsuitable for any other form of treatment because of other factors. The average age was 62 years. 42 were over 70 years and 4 over 80 years of age. Adding up our stages 1, 2 and 3, in which the disease is still clinically confined to the pelvis, 35 out of 147 patients (24%) lived three years or over, but out of 127 patients who were treated before 1944—only 8 survive the five years.

Taking all stages together of those alive

		Year			Year
10 are under		2nd	2 are under		7th
1	„	3rd	1	„	8th
2	„	4th	1	„	12th
2	„	6th			

Twelve-year case.—Female, aged 41 when treated. Colostomy and laparotomy 1938. Carcinoma of rectum fixed to sacrum and local glandular metastases. Biopsy showed adenocarcinoma. Dose 5,000 r to whole mass in thirty-nine days.

Three years later colostomy closed, P.R. now slight stricture at site of lesion. Only complaint is due to an irritable bladder, and cystoscopic examination shows telangiectasia of the mucosa, but she is quite comfortable.

Eight-year case.—Male, aged 55 when treated. September 1941 colostomy. March 1942 told he had cancer. Discharged from the Royal Navy. Treated October 1942—5,800 r to whole pelvis in thirty-four days. At this time he was ill, in pain, and had had severe hæmorrhages necessitating hospitalization. Back at work in four months and has worked since.

Seen May 15, 1950. Very well. He has no symptoms at all. Tight stricture of rectum but minimal skin changes. He had a growth completely encircling the bowel wall and filling its lumen.

We have histological proof of the destruction of the tumour in few cases, for we have not employed X-ray therapy as a pre-operative measure. The heavy radiation results in profound changes in the pelvic cellular tissues, as well as the skin and subcutaneous tissues, so that wound healing will be precarious. A woman aged 68 was treated for a carcinoma of the pelvirectal junction. The growth was clinically in an early stage, but she refused operation. Twelve months after treatment she commenced to have a return of rectal bleeding and sigmoidoscopy revealed a small ulcer at the site of the primary growth, which was thought to be a recurrence. A conservative excision was done, but the wounds never healed, she developed a coccygeal necrosis as well as fæcal fistula and died from infection. Complete examination of the bowel revealed a small focus of adenocarcinoma embedded in dense fibrous tissue.

In January of this year a man aged 64 was operated on by Sir James Paterson Ross. There was a large carcinoma of the rectum fixed to the bladder and prostate and so a colos-

tomy was done. We gave him a full course of irradiation 6,000 r to the whole tumour mass in six weeks. Three months later the growth was mobile and was removed by abdomino-perineal operation. The operation was difficult, but healing was satisfactory. There had not been sufficient time for the full development of vascular radiation changes.

Section of the ulcer shows a fibrotic ulcer on the anterior rectal wall, giving the impression of having been much larger, and having become shrunken and fibrosed. Microscopically there was a process of diffuse fibrosis extending through the rectal wall into the surrounding tissue. At the ulcer edge were a few areas of apparently viable and well-differentiated adeno-carcinoma.

The conclusion may therefore be drawn from these long survivors, from the clinical effects on the primary tumour (regression) and from histological evidence, that high-voltage radiation can affect the growth of adenocarcinoma of the rectum. This is an advance over other methods of radiotherapy—but further than this I am not prepared to go at the present time.

Recurrent Disease

70 patients have been treated in twelve years for local recurrent carcinoma of the rectum following surgical treatment of the primary. Operations varied enormously but:

23 followed perineal excision, the average time since operation being twenty-two months, the longest four years and shortest six months.

18 followed abdominoperineal excision, the average interval being twenty-five months, the longest six years and the shortest three months. 19 of these 70 (or 27%) lived three years or over, and 11 are alive to-day. Of these 1 is alive after six years.

Male aged 31. Abdominoperineal operation done by Mr. Naunton Morgan in Cairo in 1943. One year later he had a huge fungating growth the size of a fist around his colostomy and infiltrating the abdominal wall. There were also nodules along the rim of the pelvis. This was thought to be an implantation metastasis or a second primary carcinoma arising on a basis of polyposis. A transverse colostomy was done. He was treated by X-ray therapy. The growth regressed completely—he remains very well with two colostomies.

In 2 cases a local resection (wedge) of the bowel had been done for what was thought to be a papilloma. Both were malignant and recurred locally on the suture line as frank carcinomata. One is alive nine years and one six years since therapy. 3 are recent cases but 6 of these recurrent cases are over the five-year limit.

What degree of palliation can we offer?

In the long-term survivors of whom there are 14, the patients are returned to normal life and occupations. 4 have not needed a colostomy, 1 has had a colostomy closed three years after therapy. All have some degree of chronic radiodermatitis of the perineal skin, in most symptomless. A man aged 51 had a perineal excision for carcinoma of the rectum by Mr. W. E. Tanner in 1944. In March 1945, seven months later, the perineal wound broke down to form a typical malignant ulcer, but no other metastases could be detected. He was treated to a tumour dose of 5,500 r in forty days. He remains well, with a chronic perineal radio-dermatitis and a small dry necrosis. He has been on full work, which entails considerable travelling.

All these are freed of symptoms due to the primary growth although occasionally some will complain of slight mucoid discharge. A few complain of periodic irritability of the bladder due to chronic mucosal changes, but in our series bladder complications have not been sufficiently severe to be really uncomfortable.

The description of the relief of symptoms due to regression of the primary tumour is more difficult but it means so much to the patient to relieve him of symptoms such as pain, tenesmus, bleeding and discharge. From reading the case histories and following up these patients, I believe this can be achieved to a worth-while extent in some 60% of cases accepted for treatment. Thus a General Practitioner returned to his practice and worked for three years before dying, rapidly in the end, of metastases.

Another who had a proved metastasis in his liver lived eighteen months without symptoms due to his primary tumour. 2 patients, both over 80 years of age, lived two years without needing a colostomy, and died from heart failure completely free of rectal symptoms. One man with a recurrence in the stump following Hartmann's type of operation lived for four years for three and a half of which he was back on full work. A blacksmith with a perineal recurrence and inguinal node metastases returned to work symptom free for two years. An elderly clergyman was recently referred to me by Mr. E. W. Riches. This man (aged 78) had had a carcinoma of the bladder treated and now had a huge fungating carcinoma of the rectum. His life was a misery from rectal pain and bloody discharge. He was only treated six months ago, but is back at work, his only symptom being slight nocturnal frequency. He was sigmoidoscoped recently and the surgeon could find very little abnormal in the man's rectum —indeed but for the fact that he had examined him previously, he would never have known that he had had carcinoma there.

In a few patients skin, vaginal and perineal nodules have regressed, and in two a recto-vaginal fistula closed after therapy.

One can, therefore, conclude that with high voltage therapy regression of the primary tumour can occur and symptoms of inoperable carcinoma of the rectum be relieved. This relief in a few cases can be long lasting, a prolonged comfortable life, not merely existence. The treatment is a severe trial for the patient, and unless carefully administered and controlled, it is capable of great harm. It can never be repeated. To have any value it must be a full radical course the first time. Some selection of cases is essential; for patients with very advanced disease especially with infection, other methods may bring equal relief by less trying treatment, and to attempt the hopeless is worse than useless.

Finally, I would like to say that many of these patients were treated and cared for by Mr. Ralph Phillips and my predecessors on the Staff of St. Bartholomew's Hospital; and at the same time I would express my gratitude to my colleagues at Bart's and to the Staff of St. Mark's Hospital who have referred many cases to us.

Mr. Alan H. Hunt, *London:* My purpose is to present a series of consecutive cases of cancer of the rectum which is biased towards a more advanced stage of the disease, in that patients considered inoperable elsewhere often attend the Royal Cancer Hospital as a last hope. My thanks are due to the members of the Staff for allowing me to present the figures, and to my Registrar, Mr. David Wallace, and the Records Officer, Miss Kathleen Turner, for the spade work they have done in preparing the material for the Table. It is self-explanatory; but I wish to emphasize certain points.

CASES OF PROVED CANCER OF THE RECTUM ADMITTED TO THE ROYAL CANCER HOSPITAL 1945–48. TOTAL 217

GROUP I		
Radical operation alone		110
Alive without evident growth	56	
GROUP II		
Abdominoperineal excision with removal of other organs		7
Deaths following operation	2	
,, later, from carcinoma (2 and 9 months)	2	
Alive without evident growth (at 18, 24 and 40 months)	3	
GROUP III		
Tumour removable, but operation not advisable or refused		10
Treatment by Diathermy	7	
All dead in average of 13½ months (2–50 months)		
By High Voltage X-ray Therapy	1	
Dead in 10 months		
By Radium	2	
Dead in 7 and 24 months		
GROUP IV		
Abdominoperineal excision in the presence of distant metastases		19
Liver	15	
10 dead in average of 8 months (1–18)		
5 alive at 17, 27, 27, 30 and 48 months		
Prostate (dead in 25 months)	1	
Pre-aortic lymphatic deposits (dead in 25 months)	1	
Inguinal ,, ,, (,, ,, 4 ,,)	1	
Ischiorectal fossa involved (dead in 3 months)	1	
GROUP V		
Inoperable cases		39
Colostomy done in	17	
15 dead in average of 4½ months (longest 24 months)		
2 also had H.V.T. and died in 22 and 24 months		
No colostomy in	22	
21 dead in average of 2¾ months (longest 9 months)		
1 had H.V.T. and died in 18 months		
GROUP VI		
Recurrences, &c., following radical treatment elsewhere		32

In Group II there was, up to 1948, no case in which a combined excision of the rectum and bladder had been done. 4 of the 7 cases had had a panhysterectomy done together with abdominoperineal excision. Local fixity of the tumour is now not necessarily considered a contraindication to radical excision, which should be done on every possible occasion.

In Group III we have found treatment by diathermy a most valuable method of containing an accessible tumour. The woman who lived for fifty months attended for an obstructing carcinoma. Her heart condition precluded an extensive operation. Diathermy coagulation of the constricting tumour maintained her in good health (so far as her rectum was concerned) up to the time of her death from coronary thrombosis, and colostomy never had to be considered except as a remote possibility.

The results in Group IV emphasize the value of removing the primary tumour even when remote metastases are present. Particularly is this so in cases of involvement of the liver. Not only is life prolonged but the misery attendant on the primary lesion is done away with. The immediate risk from operation does not seem to be increased in that all 19 cases survived a radical excision.

The hopeless inoperable cases derived slight but significant relief from colostomy. It is probable that some would to-day have been submitted to a radical resection. Three were considerably improved for many months by high voltage X-ray therapy.

Of the purely symptomatic methods of treatment, intrathecal alcohol injections have been proved of value in relieving pain. They are usually repeated at intervals of six to twelve months.

Mr. A. Lawrence Abel, *London*:

The treatment of advanced cancer of the rectum is a problem of major surgery. Many cases seek our aid in a very advanced state and some have previously been labelled inoperable. If, however, they are tackled in a spirit of great determination many such cases are found to be not only operable, but, in fact, curable.

Even If distant metastases are present an enormous improvement in the patient's general condition leading to greatly increased length of useful, happy and comfortable life, is gained by as radical an extirpation as possible of the local condition.

The following suggestions have proved helpful in coping with many of these difficult cases:

Investigations.—In addition to the usual tests of blood, urine, biopsy, &c., further investigations are advisable in all cases of advanced cancer of the rectum. A bimanual rectal and bimanual vaginal examination should be performed preferably under a general anæsthetic. A cystoscopic examination and an intravenous pyelogram are also advisable as are X-rays of the lumbar spine, pelvis and thorax.

General principles.—It is advisable never to do a blind cæcostomy, or a blind colostomy. Every effort should be made to adopt a more active attack than the mere performance of a colostomy. No surgeon should label a case as inoperable before a laparotomy has been performed, and preferably at the time of the laparotomy at least two surgeons should be present. In all cases which have an irremovable growth (at the present day this is only 10%) everything possible should be done to avoid a colostomy. Surgical diathermy, for example, may be utilized to destroy sufficient of the growth to keep the lumen of the rectum patent. High voltage X-ray therapy may often, with advantage, be utilized to cause a shrinkage of the growth, and thus maintain adequate intestinal evacuation. Sometimes a combination of both these methods is advisable.

Types of operation.—The following types of operation are available in dealing with advanced cases of cancer of the rectum:

(1) The standard Miles' abdominoperineal excision (or modification).
(2) An extended Miles' operation in either one or two stages.
(3) Miles' (or extended Miles') operation plus part of female genitalia.
(4) Miles' (or extended Miles') operation plus Wertheim's operation.
(5) Miles' (or extended Miles') operation plus Wertheim's plus cystectomy: (*a*) partial; (*b*) total.
(6) Miles' (or extended Miles') operation plus cystectomy in the male: (*a*) partial; (*b*) total.
(7) Miles' (or extended Miles') operation plus cystoprostatectomy.
(8) Miles' (or extended Miles') operation plus loop(s) small intestine.
(9) Any of the above operations in combination with or without removal of part of the abdominal wall and a block dissection of the inguinal glands.

The extended Miles' operation.—This consists of the standard Miles' operation extended upwards by mobilization of the third part of the duodenum, and ligature of the inferior mesenteric artery close to its origin from the abdominal aorta, followed by removal of the distal third of the transverse colon, all the descending colon, and of course the pelvic colon and rectum, as in the standard operation, with all associated lymph vessels and glands.

A question of extent.—When the natural tendency for the lymphatic vessels and glands to be affected in an upward direction is considered, the question obviously arises, should not

the extended Miles' operation be done in all cases of cancer of the rectum, and not only in the advanced cases? The answer to this question is probably in the affirmative.

Aids to successful operation in advanced cases.—An operating table with a high 60° Trendelenburg tilt, and a shadowless light aimed to the bottom of the pelvis are of great help as are also very long scissors, dissecting forceps and retractors. Blunt Reverdin and blunt aneurysm needles and blunt swab dissectors are essential. Occasionally a blunt "finger-nail thimble" helps considerably.

Main points in technique.—Some of the technical points which have been found most useful are: a ligature applied to the inferior mesenteric artery either at the site of election or at its site of origin; a ligature of both internal iliac arteries immediately below the bifurcation of the common iliac artery, and a ligature of the median sacral artery.

The first of these allows a division of the inferior mesenteric artery. The last three are ligatures in continuity.

Another point is the careful stripping of the peritoneum from the walls of the pelvis and from the bladder. This allows an easy closure of the peritoneal pelvic floor and rarely, if ever, is the pelvis left non-peritonealized.

Ligature of the internal iliac arteries (anterior divisions of) is found to be of such value in advanced cases of cancer of the rectum that it has been employed in all cases of rectal cancer for many months, and its routine adoption is recommended.

The treatment of pain.—Pain may arise from bone secondaries, from pelvic metastases and from perineal metastases. In the two former, the pain may be relieved by presacral neurectomy, intrathecal alcohol and cordotomy. Testosterone does not appear of great benefit. For perineal metastases, extensive surgical diathermy is advised.

General advice.—The surgeon who wishes to do resections of very advanced cases of cancer of the rectum should learn to do the standard Miles' abdominoperineal operation and the Wertheim's hysterectomy and a total cystectomy, and the transplantation of both ureters without leakage. He should learn to do an extended Hartmann's operation from within the abdomen, i.e. excision of the pelvic colon and rectum to within 1 in. (2·5 cm.) of the anal orifice. It is helpful to be able to carry out an abdominoperineal excision entirely from the abdominal route. It is also important to learn to work quickly.

Some Illustrative Cases

Female, aged 55. Abdominoperineal excision 1932. Perineal recurrence treated by surgical diathermy 1934. Alive and well 1950. 18 years.

Male, aged 52. Excision of pelvic colon and rectum 1938. Secondary deposits remained on bladder and pelvic wall. Recurrence March 1950. 12 years.

Female, aged 28. Abdominoperineal excision September 1938. Secondaries in liver. Died from liver metastases 1947. 8½ years.

Female, aged 57. Excision of pelvic colon, small gut, vagina, June, 1943. Extensive lymphatic spread. Alive and well. 7 years.

Female, aged 24. Four years' history. Enormous mass involving vagina. Abdominoperineal excision plus part vagina September 1944. Alive and well 1950. 6 years.

Male, aged 61. Abdominoperineal excision 1939. Secondaries in liver. Died from liver metastases 1945. 5½ years.

Male, aged 60. Four years' history. Abdominoperineal excision (some pelvic growth left) 1940. Perineal recurrence: extensive diathermy 1942. Died 1944. 4 years.

Male, aged 48. Abdominoperineal excision March 1945 (secondaries in liver now causing symptoms). 5½ years.

Female, aged 60. Abdominoperineal excision (secondaries in liver) February 1946. Died March 1950. 4½ years.

Female, aged 68. Abdominoperineal excision July 1946. Secondaries in glands of groin. Alive and well 1950. 4 years.

Male, aged 51. Abdominoperineal excision (secondaries in liver) February 1947. Alive and well 1950. 3¾ years.

Male, aged 57. Abdominoperineal excision (secondaries in liver) December 1947. Alive and well 1950. 2¾ years.

Section of Laryngology

President—R. D. Owen, B.Sc., F.R.C.S.

[*May* 5, 1950]

DISCUSSION ON THE ROLE OF SINUSITIS IN BRONCHIECTASIS

J. C. Hogg: The existence of a close connexion between infective disorders of the upper and lower air passages is now accepted as a commonplace, but it was not until well on into this century that papers on this topic began to appear in the literature. In this, as in so many other aspects of laryngology and rhinology, StClair Thomson (1914) was among the first to draw attention to this significant relationship.

Definition of Bronchiectasis and Sinusitis

Bronchiectasis may be defined as a condition of permanent dilatation of one or more bronchi. Sinusitis is a much more difficult disorder to define, since the sinuses are capable of all sorts of variations from the normal, not necessarily of a permanent nature but to which the label sinusitis is in practice commonly applied. For the purpose of the present paper, transient infections of the sinuses will be ignored, and only those more chronic inflammatory disorders will be considered which are characterized by the production of a persistent purulent, or mucopurulent discharge, or by the presence of gross hyperplastic changes in the mucosa.

Unity of the Upper and Lower Respiratory Tracts

In considering respiratory infection in general, it is false and arbitrary to separate from each other those parts of the respiratory tract which are situated above from those which are situated below the level of the larynx. For they both serve the same physiological purpose of bringing oxygen to the lung alveoli after it has been warmed, moistened and filtered in its passage over their mucociliary epithelium. It is not, therefore, unreasonable to suppose that they will both be subject to invasion by the same infective organisms, although the response may vary with the anatomical arrangement. In comparing the upper and lower respiratory tracts, in their common reaction to disease, Hodge (1938) pointed out that the most notable feature leading to failure of resolution is interference with drainage, a factor of paramount importance in the ætiology of both sinusitis and bronchiectasis.

Ætiology of Bronchiectasis

It is commonly taught that there are two types of bronchiectasis, congenital and acquired. Congenital bronchiectasis, if it exists at all, which is disputed by such authorities as Kerley (1936), and Maurice Davidson (1948) is, at any rate, of considerable rarity. It has been supposed that fœtal abnormalities might account for some of these so-called congenital types, of which the two main would appear to be congenital cystic disease of the lung, otherwise known as honeycomb lung, and Kartagener's syndrome, or triad. So far as I have been able to discover on looking through the records of some of these cases of congenital cystic disease of the lung, they resemble those with acquired bronchiectasis in also being prone to infection of the paranasal sinuses.

Kartagener's triad of situs inversus viscerum, bronchiectasis and sinusitis, with absent or ill-developed frontal sinuses is an interesting syndrome, since it associates a freak of development with gross infection of the bronchi and nasal sinuses. In the case illustrated by Figs. 1, 2 and 3 the patient was a female aged 10, a patient of Dr. W. E. Lloyd's, to whom I am indebted for permission to quote the records.

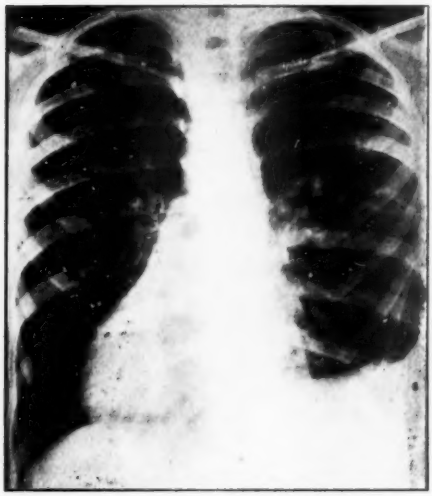


FIG. 1.—Kartagener's triad; note dextrocardia.



FIG. 2. — Kartagener's triad; bronchogram showing situs inversus with left lower and middle lobe bronchiectasis.



FIG. 3.—Kartagener's triad; note opacity of antra and absence of frontal sinuses.

History.—Cough and sputum since babyhood. Sputum never offensive or blood-stained. Has missed much school.

Condition on examination.—Dextro-cardia, rhonchi over left base, in front and behind.

Plain X-ray of chest.—Transposition of viscera.

Bronchography.—Shows dilatation of the bronchi in the left lower and middle lobes.

X-ray of sinuses.—Frontal sinuses do not appear to be developed. Appearances in the antra suggested bilateral infection.

Treatment.—Antral lavage and removal of tonsil remnants and adenoids. Left lower and middle lobectomy by Mr. C. Price Thomas.

So far as I am aware, no satisfactory explanation of this condition has yet been put forward.

The causative factors in acquired bronchiectasis.—It used to be thought that severe or protracted inflammation of the bronchial walls, associated with obstruction of the lumen by secretions, foreign bodies, or pressure from without by cicatrization, mediastinal tumours, or aneurysms was the responsible mechanism for producing bronchiectasis. Research of recent years has shifted the emphasis from the infective to the mechanical factor, as the result of information gained by the study of a large series of X-ray films, both plain and after bronchography. In 1938, Lander and Davidson showed that atelectasis, or perhaps the better word is collapse of a lobe, or a segment of a lobe, is extremely common in lower respiratory infections. They also showed that bronchograms done during the phase of collapse tend to reveal dilatation of the supplying bronchi or bronchioles. Furthermore, that with the re-expansion of the area of collapse the bronchi usually revert to their normal calibre. The explanation of this phenomenon would appear to be that in a rigid or semi-rigid box such as the thorax, with its negative intrapleural pressure, any diminution in volume of the lung tissue has to be compensated by mediastinal shift, raised diaphragm and an outward pull on the elastic-walled bronchi. So long as the latter are not fibrosed, they will dilate and then return to normal as the area of collapse re-expands. Failure of re-expansion and superadded infection, possibly in some cases due to aspiration from pre-existing or co-existing sinusitis, will explain the ætiology of many cases of acquired bronchiectasis. Likewise it explains how the more benign "dry" bronchiectasis described by Wall and Hoyle (1933) can exist for years before being transformed into the more serious wet variety.

Allergy

It will be seen that if we accept the views of Lander and Davidson (1938), the mechanical factor is the most important in the production of bronchial dilatation. Plugs of viscid mucus, giving rise to bronchial block, cause areas of collapse which in turn produce traction on the walls of the contained bronchi. Davison (1944) put forward the view that allergy plays a major role, both in the production of bronchiectasis and in the frequently associated sinusitis. Using as his criteria the presence of nasal polypi, and eosinophilia, he demonstrated allergy in every one of his cases in which sinusitis and bronchiectasis co-existed. He showed that in the child, 1 mm. of œdema in a 6 mm. bronchus reduces the lumen to 44% of normal, whereas 1 mm. of œdema in a 3 mm. bronchus reduces it to a mere 11% of normal. He, therefore, attributed the increased frequency of left-sided bronchiectasis to the relative narrowness of the left bronchi. Allergy can thus produce all the factors needed for the development of bronchiectasis, namely viscid secretions, narrowing of the bronchus due to œdema, and a tendency to co-existing nasal sepsis. On the whole, Davison is in agreement with Wasson's theory of broncho-sinusitis disease as the initiating factor, adding allergy as a cause for incomplete resolution. Alternatively, he believes that the whole respiratory tract in allergy is sensitized, in which case it is only a matter of time before sinusitis develops, if it follows the bronchiectasis.

Sinusitis as a Cause of Bronchial Infection

Much speculation has existed as to the precise part which the nasal sinuses play in infection of the lower air passages. There is little doubt that in both acute and chronic infections of the lower air passages, infections of the nose and sinuses play an important part. The classical observations of Graham (1931) showed that in cases of bronchial fistula the discharge would become purulent and copious during an attack of acute sinusitis, where there was normally only a very slight discharge from the external opening. With the resolution of the sinusitis the bronchial fistula would return to its previous state, thus affording clear proof of the effect of paranasal infection on the bronchial mucosa. It has not been entirely settled, however, at what stage sinusitis becomes associated with bronchiectasis. There are three possibilities: (1) That the sinusitis precedes the bronchiectasis, to the development of which it contributes. (2) That sinusitis and bronchiectasis develop synchronously, as put forward by Wasson (1929) in his paper on broncho-sinusitis disease. Recently, Paton Philip (1948) has published observations on a very large series of radiographs demonstrating partial atelectasis of the lung, associated with X-ray evidence of paranasal sinus inflammation. He has shown that with the successful treatment of the sinusitis the collapsed segment re-expands. (3) That chronic sinusitis develops secondarily to bronchiectasis. There are certain

arguments in favour of this third hypothesis. Bronchiectasis developing as the result of foreign body, or mediastinal tumour has, in the speaker's experience, been followed by a severe sinusitis in a patient previously known to have had healthy upper air passages. There is little doubt that constant droplet infection of the nasopharynx and of the nasal passages can occur, and in this connexion an interesting investigation is being carried out at the Brompton Hospital, by Professor F. C. Ormerod. He has provided me with X-ray films of the nasal sinuses, showing the presence of lipiodol in small quantities in the nasal passages in 4 out of 15 cases, who were X-rayed soon after the instillation of lipiodol for bronchography (Fig. 4). It will be remembered that Proetz (1932), in his classical experiments on the air



FIG. 4.—Traces of lipiodol in nose and antrum after bronchography.

currents in the nose, demonstrated that the expired air currents deflected by the posterior end of the middle turbinal pass beneath it, and, in that way, are in close communication with the ostia of the nasal sinuses. It is probable that, in this way, infection can be conveyed from the infected bronchus to the nose and sinuses (Ebbs, 1937; Lemon, 1926).

POSSIBLE ROUTES OF INFECTION

The connexion between the upper and lower respiratory tracts (Ormerod, 1941) may be by four possible routes: (1) Aspiration. (2) Lymph stream. (3) Blood stream. (4) Direct continuity.

(1) *Aspiration.*—A droplet infection through the nose and sinuses to the lower air passages is an established fact, and there exists experimental proof that radiopaque substances can pass from the nose and sinuses to the bronchial lumen.

(2) *Lymph stream.*—It has been shown that dye-stuffs placed in the paranasal sinuses can be found in the lymphatics of the chest. The lymphatic connexions between the nose and the chest are somewhat complex, but it is possible that organisms may follow this route.

(3) *Blood stream.*—Whereas this route is favoured by many authorities as the method of origin of lung abscesses, it is doubtful whether it plays any part in the development of bronchiectasis.

(4) *Direct continuity.*—The work of Wasson (1929), and later of Paton Philip (1948), goes to show that bronchiectasis and upper respiratory disease are frequently the result of some generalized inflammatory process involving both divisions of the respiratory tract.

INCIDENCE OF SINUSITIS IN BRONCHIECTASIS

In reporting their findings in cases of bronchiectasis, Clerf (1934) found sinusitis in 82·4%, Hodge (1935) in 75%, Watkins (1936) in 89·3% and Farrell (1936) in 75–80%. Fletcher (1935), on the other hand, investigated 100 cases of bronchiectasis, of which 48 were children and 52 were adults. There were no cases of sinusitis in the children, and only 4 cases in the adults. His findings are unusual and not in keeping with all other reported series.

Ormerod (1941) analysed a group of 40 cases of bronchiectasis. 22 showed some inflammatory lesion of the nose, paranasal sinuses or pharynx; in 17 of these, or 42·5%, the infection was found to be in the sinuses.

A recent survey carried out by the speaker of 110 cases of bronchiectasis referred to the Throat and Ear Department of the Brompton Hospital during the past three years showed that 67 of these, or 60·9%, had evidence of sinusitis, 24, or 21·8%, were suffering from infection of the tonsils or adenoids, and 6, or 5·4%, from chronic suppurative otitis media. The diagnosis of sinusitis was confirmed in all cases by X-ray and proof-puncture. The remaining 13 had no demonstrable lesion of the upper respiratory tract.

Sex.—Of the 110 cases, 57 were female and 53 male.

Age.—The following age-groups show conclusively that bronchiectasis is a disease of early life. No less than 72, or 65·4%, are represented by the age-group 1–20.

Age-groups			
1–10	34	or	30·9%
11–20	38	or	34·5%
21–30	19	or	17·3%
31–40	14	or	12·7%
41–50	5	or	4·6%
	110		

Lobectomy or pneumonectomy was carried out in 49 cases. Of these 49 cases, 28 or 57·1% had operative treatment for sinusitis. Antrostomy was performed on 9 cases, ethmoidectomy on 3, and repeated antral puncture on 16. 2 mastoid operations were also carried out.

Views on the Treatment of Sinusitis Complicating Bronchiectasis

Ideally one should aim at complete cure of paranasal sinus infection in the bronchiectatic, in order to relieve him of this added toxæmia, as well as to lessen the risk of constant reinfection of his already damaged lower air passages. It is well known that "dry" bronchiectasis will exist for years with very little consequence to the victim's general health, so that it would appear to be particularly important to eliminate any upper respiratory infection in that type of case. Some experience, however, of the problem of recommending the best form of treatment of sinus disease in bronchiectasis has led the speaker to the firm conclusion that no hard and fast rule can be laid down. Each case must be considered individually, in full consultation with the physician or surgeon concerned. To illustrate my own views on the general principles of treatment, I will take as a typical example the case of a young adult patient found to be suffering from established suppurative bronchiectasis, which is apparently still confined to one or two lobes. Investigation of the upper air passages may reveal extensive involvement of all the sinuses, often with polypoid changes in the ethmoid, and radiologically opaque frontal sinuses. The nasal symptoms in a case of this type are usually minimal, and only on questioning do they admit to nasal obstruction and discharge. Pain is most uncommon. As a candidate for lobectomy with a reasonable ultimate prognosis, it would, in that case, be highly desirable to eradicate the nasal infection, even if that involves extensive sinus surgery, possibly even radical ethmoidectomy and antrostomy. In that type of case the external fronto-ethmoid operation of Howarth, Seiffert or Ferris Smith type has given gratifying results. These radical procedures, if carried out one side at a time, appear to carry less shock with them than many a less complete intranasal operation. The explanation is, of course, that the key to comfort and safety after sinus surgery is the presence of free drainage.

Another common type is the patient with extensive bronchiectasis involving both lungs, for whom there is no hope of eradicating the disease by surgical means, and who likewise has a gross nasal sepsis. It is unjustifiable here to contemplate any radical measures. These patients are sick people, and poor surgical risks, with a reduced expectation of life. Since their bronchial disease is too advanced for cure by surgical operation they will continue to cough up infective material for the rest of their days. This will mean a constant bombardment of their postnasal space, and, as I believe, probably of their nasal passages as well, precluding any hope of avoiding constant reinfection of the nose and sinuses. The rhinologist should content himself here with the provision of adequate, permanent intranasal drainage of infected maxillary antra, preferably carried out under local anæsthesia, together with the removal of any nasal polypi which may be present. It is surprising to find how much toxæmia can be relieved by such simple intranasal measures, although there sometimes appears to be little or no subsequent change in the quantity of the nasal discharge. Put briefly, where there is a chance of curing the pulmonary suppuration, nasal surgery should be as complete as is required, but otherwise a conservative policy is the best.

Treatment in children.—For anatomical reasons they are less likely to suffer from such gross degenerative infections of the sinuses, since they have comparatively poorly developed ethmoidal cells and frequently absent, or rudimentary frontal sinuses. By and large, it is the maxillary antrum which has to be treated in children, although this statement should not

imply that there are not difficulties that the rhinologist will encounter in this field. Apart from all general measures to be carried out in collaboration with the physician, there are various local treatments at our disposal. Naristillæ of a decongestive type to promote drainage are used, such as ephedrine 0·25% solution in isotonic saline. This solution can also be used for displacement treatment of the sinuses by the Proetz technique, as can a solution of penicillin in saline, provided that the dilution of the former is kept to about 2,000 units per ml. Higher concentrations are unnecessary, and have been found to possess irritative properties if used repeatedly. By means of the Proetz displacement technique a considerable improvement can often be effected in chronic cases, particularly in ethmoidal disease. Crooks (1938) and others have shown that antral puncture and lavage, under local anæsthesia, is a simple procedure applicable to even quite small children, when carried out in a well-run clinic. Recently a promising substitute for repeated antral puncture has been developed in the method of perfusing the antrum with antibiotic solutions, or isotonic lotions through a fine polythene tube, introduced into the antrum through a Lichtwitz cannula (Fig. 5).



FIG. 5.—Perfusion of antra through indwelling polythene tubes.

This tubing appears to have no irritative effects on the nasal mucosa. Assisted no doubt by the fact that children naturally possess far greater recuperative powers than adults, this antral perfusion method promises to become a valuable method of treatment in the conservative management of the difficult problem of chronic sinusitis in children. It should certainly prove to be of value in the preparation of a child for lung operation, and it can again be employed, after successful lobectomy, to treat any residual sinus disease.

There will remain, however, a small hard core of cases in children, whose antral infection, fed as a rule by coexisting ethmoidal suppuration, will demand operation. For choice I elect to perform an intranasal antrostomy rather than to operate via the canine fossa, in view of the considerable effects of the latter operation upon the development of the maxilla and the permanent upper teeth. However antrostomy is carried out in children, nature does her best to defeat our well-intentioned efforts by stenosing, and all too often, by finally closing the antrostomy opening, and it is not uncommon for repeated drainage operations to be required.

Anæsthesia for the surgical treatment of sinusitis in bronchiectasis.—Local or regional anæsthesia is to be preferred, but in many cases general anæsthesia has to be resorted to. Pre-operative measures must include adequate tipping to empty the tubes as far as possible, and in severer cases preliminary bronchoscopy and suction is to be recommended. There is, otherwise, the danger of an alarming flooding of the air passages during the induction of the anæsthetic, and even if this does not occur there is the notorious difficulty of keeping them adequately oxygenated throughout the operation. Thanks, however, to the skill of modern anæsthetists these difficulties can be surmounted.

The time factor for sinus surgery in cases where lobectomy, or pneumonectomy, is contemplated must be discussed with the surgeon. A vicious circle has to be broken, as unquestionably the infected bronchi reinfect the nasal passages, and yet so long as there is a sinusitis the success of lobectomy and pneumonectomy may be jeopardized. On the whole, I believe that with the aid of antibiotics, it may be best to treat the pulmonary suppuration and to follow with the sinus surgery subsequently. Certainly that is so where the nasal operation is likely to be of an extensive nature.

I would like to express my indebtedness to the Staff of the Brompton Hospital for their permission to use the records and X-ray films of their patients, and particularly to Professor F. Ormerod.

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R. C. Brock: Two aspects of the problem of sinusitis in bronchiectasis which should be considered are: (1) The true features of the interrelation between sinusitis and bronchiectasis; (2) the treatment of the two conditions as they occur together.

(1) *The interrelation of sinusitis and bronchiectasis.*—There can be no doubt that there is a true association between sinusitis and bronchiectasis. Whether the sinusitis is the primary event and the bronchiectasis follows or vice versa; or whether both conditions arise simultaneously, it is probable that at one time or another all 3 modes of infection occur and sometimes in considering the difficulties of assigning the role of primary importance one is reminded of the other age-old problem "which came first, the chicken or the egg".

The important interrelationship between simultaneous or consecutive infection of the upper and lower respiratory passages is known to all of us and is only too often seen in the common cold and other acute respiratory infections, but there is little real evidence to show that sinusitis is the usual primary lesion when it is found to exist with bronchiectasis. For one thing sinus infection in big communities, such as in our large industrial cities, is a very common condition, far more common than the incidence of bronchiectasis. In other words, sinusitis can often exist without bronchiectasis.

A common and direct relationship, in which the sinusitis may well be the primary or predominating lesion, is certainly seen between sinusitis and *bronchitis*, whether acute, recurrent or chronic. There is ample clinical observation and experience to support this. The relationship between sinusitis and bronchiectasis, a condition in which permanent and often severe secondary anatomical changes are present, is, however, quite different; this is principally and most significantly because the ætiology of bronchiectasis, with its important local changes, is different from simple bronchitis which can be a superficial and recoverable condition. Bronchiectasis is often associated with a local determining cause or various local determining factors that cannot possibly be directly caused by sinusitis. Amongst such factors are bronchial obstruction, either temporary or permanent, from tumours, foreign bodies, strictures or external compression from enlarged lymphatic glands, &c.; various congenital factors may also be responsible.

Bronchiectasis can result from the damage inflicted by a severe lung infection and in this way it could be caused by spread of infection from a pre-existing sinusitis, but it is doubtful if this is the usual course of events. A severe lung infection that progresses to an established bronchiectasis is more commonly seen in association with some illness such as whooping cough or measles, or in adults in association with a severe pneumonic condition in which sinusitis is not evident except as a possible minor concomitant.

Lung infections more serious than a simple acute or recurrent bronchitis can certainly be caused by sinus infection and the probable mode of spread can be demonstrated to be a process of bronchial embolism or the inhalation of purulent material into the bronchial tree, usually during sleep or deep narcosis. The mechanism can be readily demonstrated by the instillation of lipiodol into the nose and its later demonstration by radiography within the lungs. Such an event most commonly gives rise to a pneumonic attack with resolution, or to a frank lung abscess. It is not usually followed by the development of a lobar or multisegmental bronchiectasis giving the clinical state of bronchiectasis as we understand it;

only occasionally will the chance presence of a specially unfavourable organism give rise to severe and permanent bronchiectatic changes of this type.

Conversely we find that in cases of bronchiectasis which have certainly arisen from some local factor within the lungs, the incidence of associated sinusitis is high.

It has just been mentioned that it is simple to demonstrate that material from the nasal cavities can gravitate into the bronchial tree during sleep or narcosis. The reverse process can also be shown to take place. If a bronchiectatic patient with a severe productive cough is watched while in a paroxysm of coughing it will be seen that pus comes not only into the mouth, but also runs into the nose and pours out through the anterior nares. If, after a bronchogram, a patient is asked to cough and empty his bronchi and then the nasal sinuses are radiographed, it can be shown that the opaque oil has actually entered the sinuses themselves and may give a very good outline picture of one, two or several of the various groups. In one patient a bronchogram was followed by fever and pain and discomfort in the nose in the region of the right maxillary antrum and a radiograph two days later showed the antrum half full of lipiodol. It needs little imagination in such cases to picture how an acute sinusitis can be caused if pus collects in the sinuses in a similar way; if a chronic infection is not caused by one such episode the patient with bronchiectasis who is coughing up pus each and every day is regularly exposing his nasal sinuses to infection by this mechanism.

We can, therefore, conclude that whereas sinusitis is a frequent cause or accompaniment of the more superficial or transitory catarrhal lung infections, it does not usually give rise to established bronchiectasis. Bronchiectasis with the regular or intermittent production of purulent sputum is, however, a powerful potential cause of sinus infection and the frequent association of sinusitis with bronchiectasis arising primarily within the lungs indicates that the sinusitis is the secondary event, following and complicating the bronchiectasis.

(2) *Treatment of associated sinusitis and bronchiectasis.*—The nature of the relationship between the two conditions, once it is defined and accepted, is of great practical importance in guiding the treatment to be adopted.

The first feature to consider is the supposition that sinus infection can cause acute, recurrent or chronic lower respiratory infection. If bronchiectasis is present, from whatever primary cause, it is clear that a sinusitis may initiate, maintain or aggravate infection within the bronchiectatic region. It is, therefore, clear that successful treatment of the sinusitis may result in mitigation or removal of the infection present in the bronchiectatic lung. The morbid anatomical changes in the bronchi will persist, but if a source of constant or recurrent infection from above is removed and bronchial drainage is aided by posture and other physical treatment, the productive cough and other symptoms may be so relieved, especially to-day with the additional help of penicillin, &c., that the patient may be rendered quite comfortable and removal of the bronchiectatic lobe or lobes is unnecessary.

This happy event is not often seen, probably chiefly because the permanent changes in the bronchi are such as to make it difficult or impossible for the local infection to resolve. Large complicated bronchiectatic cavities in which stagnation and intermittent obstruction occur are unfavourable, and cough and sputum continue, often accompanied by severe exacerbations. We are all familiar with the patient who, in spite of all the most carefully applied expectant management, continues to raise purulent or even offensive sputum daily, often in large quantities. It is in such cases that the most severe and most intractable forms of chronic sinusitis are found and from the arguments put forward above, it is probable that the sinuses are being constantly reinfected from the lungs, quite apart from they themselves having developed permanent changes promoting chronicity. It is no longer a question of the sinuses infecting the bronchi, unless it be that the two established conditions work together and on each other for evil. If this hypothesis be correct it is clear that treatment directed to the permanent relief of sinusitis is foredoomed to failure. In practice this is frequently found to be the case. I think that anyone, whether physician, thoracic surgeon or rhinologist, who has had a wide experience in these cases, will agree that chronic sinusitis existing with chronic bronchiectasis is often totally incurable so long as the bronchiectasis remains unrelieved. This important and relatively easily understood state of affairs is only too frequently not appreciated with the result that over-zealous, and one might also say futile, attempts are made to eradicate a chronic nasal sinusitis that fails to show any permanent response.

It is important in dealing with these cases of associated resistant sinusitis and bronchiectasis to consider the patient as a whole and not as an object with an infected nose. I think I may say without causing undue offence, that there is a danger that the inexperienced rhinologist may concentrate his attentions too much on the nose to the exclusion of the patient as a whole. I have found this is particularly so with the surgeon who has only recently encountered such cases. If he is asked to see a patient who has bronchiectasis and to give a report on the condition of the sinuses and his advice on treatment he may state that all the sinuses are infected and that numerous bilateral operations of a radical nature are needed. If a patient

is to undergo lobectomy or pneumonectomy, possibly even bilateral lobectomy in the more severe cases in which more severe sinusitis is often found, it is quite a severe additional ordeal if he is also to undergo multiple nasal operations. It is the duty of the thoracic surgeon concerned to try and hold a balance in this matter. In such cases I always ask the rhinologist what result he expects from his severe plan of campaign. He may be both knowledgeable and frank and admit that success is uncertain or unlikely but that the state of the sinuses indicates this treatment should be advised. In such circumstances one must exercise discretion in considering the case as a whole as to how much should be done to the nose; the final decision should come from the surgeon or physician who is primarily responsible for the treatment of the patient.

If I am told that success is guaranteed my practice is to discuss the problem directly with the most senior rhinologist available. It is usually the more junior and less experienced man who is found to be so optimistic about the outcome of radical sinus surgery in association with bronchiectasis. The more experienced rhinologists are usually less dogmatic about the certain benefits and we usually agree on a less severe programme. If, of course, a clear and authoritative case is stated for a radical procedure, then it must and should be accepted. It should be accepted though only after all the implications have been frankly discussed.

In practice one finds that in many of these severe cases of co-existing chronic sinusitis and bronchiectasis it is almost impossible to clear up the nasal infection permanently and completely until the bronchiectasis has been cured.

Our policy, therefore, should be some simple treatment of the sinus infection, extending to aspiration or some form of simple surgical drainage. If this is successful in alleviating the sinus infection much will have been gained and even if the infected bronchiectasis continues unimproved its removal by operation is more satisfactory if the nasal sinuses are clear and dry. If a complicated chronic sinus infection is present that does not respond to the less severe measures then the bronchiectasis should be operated upon and the condition of the nasal sinusitis reassessed after the patient has been relieved of his constant production of purulent sputum, which may well be the most important factor in maintaining the chronic nasal sinus infection that has hitherto resisted all treatment.

Unfortunately, in some cases even after the lungs have been successfully dealt with, the changes in the sinuses may have become so firmly established that complete cure is difficult or impossible to achieve.

If the disease in the lungs is unsuitable for radical surgical treatment, either on account of its extent or of some personal factor in the patient, then the rhinologist who succeeds in permanently and completely eradicating an associated chronic nasal sinusitis will indeed have achieved a triumph.

W. Paton Philip stressed the importance of the co-operation of the chest physician and the ear, nose and throat surgeon in the examination of these cases. A routine examination of the chest should include the examination of the nose, nasopharynx and the sinuses.

In a large number of cases, especially in children, referred to him for opinion, he had found sinus infection associated with X-ray evidence of atelectasis or collapse of certain lobes or bronchopulmonary segments. During the past twenty-six years, he had routinely X-rayed the paranasal sinuses in every case referred to him and stressed the importance of chest X-rays in the lateral and lordotic views.

It had been estimated that the daily secretion of mucus from the sinuses normally amounted to 1,500 c.c.

He agreed with Dr. Maurice Davidson on the importance of pulmonary collapse or atelectasis in the ætiology of bronchiectasis and showed a series of lantern slides of X-rays of cases where there was at one and the same time evidence of sinus infection and collapse of certain bronchopulmonary segments, including especially right mid-lobe, segments of the lower lobes and the lingula of the left upper lobe—just those segments commonly affected by bronchiectasis.

With early and efficient treatment of the sinuses, the pulmonary collapse resolved. He was indebted to Mr. Walford, E.N.T. surgeon of Cambridge, for co-operation in the treatment and they often observed the evolution and the complete resolution of these cases. Transillumination and proof puncture were often deceptive in diagnosis.

He included in his series in children only those cases with negative tuberculin reactions, where the collapse could not have been brought about by the presence of tubercular glands, and suggested that the collapse was brought about by infected material from the sinuses tracking downwards. He stressed the importance of long convalescence in the fresh air, with breathing exercises strictly through the nose during both phases of respiration, if possible under the guidance of a trained physiotherapist.

Breathing exercises ensured the all important ventilation of the sinuses and re-expansion of the collapsed areas in the lungs.

Maurice Davidson said that it was most important that they should regard the patient as a whole, and not in watertight compartments. The question whether sinus infection was antecedent or succedent to bronchiectasis was one of academic interest, rather than one of practical importance. What the practitioner must realize was that knowing that the two were so closely associated he must, in planning the course of treatment in bronchiectasis, take both conditions into account and deal with each individual case upon its merits.

He quoted a case of a young Welsh student sent to him from the country with severe general toxæmia. This patient had bilateral bronchiectasis and there was no question of any attempt at radical thoracic surgery. Throughout the conduct of this case at home it had not apparently occurred to anybody to consider the upper respiratory tract at all. Although the lad had lost weight and was febrile, had constant sweating, and was coughing up large quantities of purulent sputum, no one had looked at his nose and throat. On investigation at Brompton he was found to have a very severe chronic infection of both antra. Radical thoracic surgery was not possible, but the improvement in the patient's general condition, the increase in weight, and the clearing up of the toxæmia after drainage of the sinuses were such that this lad went back home to his studies an absolutely different person.

He also cited the case of a man with a large tubercular cavity, a positive sputum, extremely hoarse and very toxic and febrile. Both vocal cords were injected. This was thought to be a simple chronic laryngitis secondary to badly infected tonsils. Mr. J. C. Hogg, in consultation, was in agreement with this view and they had a discussion as to whether they should tackle the tonsils first and later consider an upper thoracoplasty to close the cavity, or vice versa. Mr. Brock said that if he had to do the thoracoplasty he would rather do it in the presence of a healthy upper respiratory tract; Mr. Hogg said if he had to enucleate the tonsils he would rather do so when the chest condition had been stabilized. It was ultimately agreed that the best thing was to treat the upper respiratory tract first. After enucleation of the tonsils the laryngeal condition cleared up completely, and the patient was discharged home with the idea of readmission at a later date for a thoracoplasty. Eventually, however, the cavity got progressively smaller until it was finally obliterated and the man got perfectly well.

Sometimes one had to assess a case of bronchiectasis and decide whether a lobectomy was or was not necessary. This should always be done with reference to the particular patient, and if it was concluded that a lobectomy or pneumonectomy was not immediately necessary the need for tackling any chronic sinus infection was frequently overlooked by the general practitioner and even by many consultant general physicians who by this time ought to know better. Dr. Davidson pleaded for more consideration of the important principle of relative values in each individual case.

The following also spoke: **H. V. Forster, J. A. Harpman, L. Graham Brown, C. Hamblen-Thomas, E. Cowper Tamplin, The President** (R. D. Owen).

J. C. Hogg, in reply, said that radical operations in children were very seldom necessary, particularly external operations. The reason was an anatomical one. These children as a rule did not have any frontal sinuses until the age of 8 or 10, and even then they were somewhat rudimentary. There might be an occasional case for doing an operation of that nature and in such an event he would not hesitate to do it and he did not think it would have any adverse effect.

Dr. Davidson had described how essential it was that there should be team-work in these cases. He would go further than that and include Mr. Hamblen-Thomas's plea that a physician should be in control. The physician alone could take the broad view in these cases.

R. C. Brock, also in reply, said that he agreed as to the need for prolonged convalescence. It was no good getting bronchiectatic children into hospital for a short time for operating on the nose or the lung. To deal with them satisfactorily one had to be very generous so far as days spent in hospital were concerned. It was much better to have them under conditions which would enable them to get fit.

There was no doubt that the results of lobectomy were influenced by the presence or absence of sinus infection. It was best to operate on the lung after the sinuses had been made clean by the throat surgeon.

On the question of cricothyroid puncture for bronchography, he felt strongly that it should never be done. It was unfortunate that only in this country, so far as he knew, was this method still in use.

Section of Laryngology with Section of Otology

COMBINED SUMMER MEETING HELD AT CARDIFF

LARYNGOLOGICAL SESSION

[*July* 1, 1950]

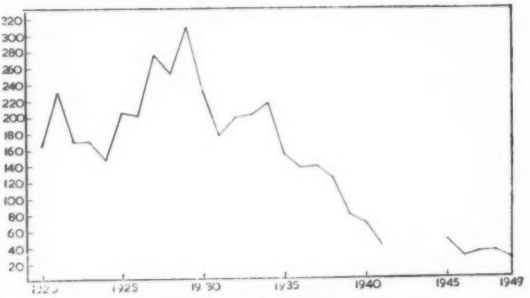
Chairman—R. D. OWEN, F.R.C.S.
(President of the Section of Laryngology)

A Review of Tuberculosis of the Upper Air Passages During the Past Thirty Years and its Treatment by Streptomycin

By F. C. ORMEROD, F.R.C.S.

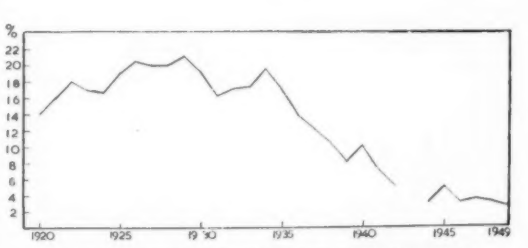
A GREAT change has come over the problem of tuberculosis of the upper air passages during the past thirty years. In 1935 Scott Stevenson published his "Recent Advances in Laryngology and Otology" and in 1937 StClair Thomson published the fourth edition of his "Diseases of the Nose and Throat". They both quoted from the vital statistics for 1933 and both assumed that one in every three patients suffering from pulmonary phthisis developed tuberculosis of the larynx at some stage of the disease. An investigation of the records at the Brompton Chest Hospital from 1921–35 suggested that the proportion was nearer one in four and was tending to fall. This reduction has continued steadily, except for a slight rise during 1941, until a proportion of 2½% was reached in 1949—one-tenth of what it had been twenty years previously.

The following graphs show the total number of cases of tuberculosis of the larynx seen at Brompton (Graph 1), the proportion of the total number of phthisical patients so affected (Graph 2) and the total number of cases seen at King Edward VII Sanatorium at Midhurst (Graph 3). There is a gap in the graph for Brompton during 1942–43–44 owing to the loss of some of the records, but this does not appear to alter the general picture.



GRAPH 1.—Cases of tuberculous laryngitis, Brompton Hospital.

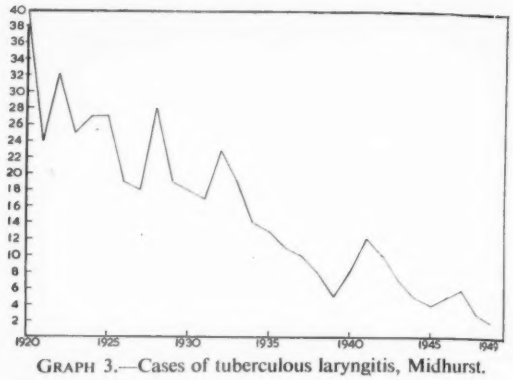
At Brompton there was a rise both in the total numbers and in the proportion during the 1920–30 decade. These figures reached a peak during 1929 and from then have fallen steadily except for a slight rise between 1930–34, which coincides with the financial and economic depression of that period, and a similar rise in 1940–41 which coincides with the air attacks on this country and the subsequent frequent disturbances and forced removals of patients from one part of the country to another and also with the worst period with regard to rations.



GRAPH 2.—Percentage of patients with tuberculous laryngitis, Brompton Hospital.

The Midhurst figures are very similar and show a curve, which, though less regular on account of smaller numbers, is comparable to those at Brompton.

The changes in the figures for the larynx are repeated in those for the pharynx, tongue, mouth and nose. As the proportion of tuberculous lesions in these areas, all taken together, was, at the worst period, only two-thirds of 1%, they have now become rare to an extent that they are only an occasional experience.



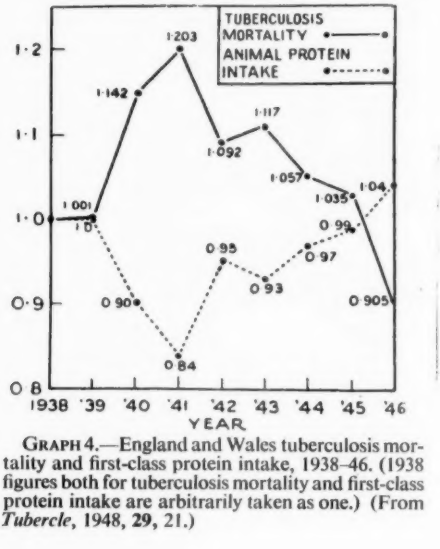
GRAPH 3.—Cases of tuberculous laryngitis, Midhurst.

In America Dworetsky and Ruck showed that the percentage occurrence of tuberculous laryngitis in the living was as follows: 1914, 25·6%; 1934, 14·6%; 1941, 3·6%.

In 1914 Fetterolf reported that in his series of autopsies of phthisical patients 83% had a tuberculous lesion of the larynx. In 1946 Auerbach reporting a series of similar autopsies found only 37·5%—a reduction of more than half. These figures have established the fact that there has been during the past twenty or thirty years a steady decrease in the number of tuberculous lesions in the upper respiratory areas, until they are becoming relatively uncommon.

The social problem of tuberculosis has not been reduced to a similar degree and it has been a matter of continued interest as to why the incidence of these secondary manifestations of pulmonary phthisis should be steadily lessened even during the war with all its disturbances, privations, indifferent and often unsuitable food, interruption of treatment and other difficulties. Probably a number of factors share responsibility for this change in the incidence of one manifestation of the disease, a lessening which has far outstripped the improvement in the general aspect of tuberculosis. There has undoubtedly been a great improvement in the general level of social welfare. The earning capacity and the purchasing powers of the poorer strata of society has been increased steadily for many years. They are able to buy and have bought better food—better in quality, in quantity and also in suitability and the issue of free meals and almost unlimited milk to school children has added vastly to this improvement. It was only in 1940–41 that there was any real shortage of food and at that time there was an actual increase in the tuberculosis mortality and morbidity.

In Graph 4 the variation in the amount of first-class protein in the rationed diet in Great Britain and also in the mortality from tuberculosis are set out.



GRAPH 4.—England and Wales tuberculosis mortality and first-class protein intake, 1938–46. (1938 figures both for tuberculosis mortality and first-class protein intake are arbitrarily taken as one.) (From *Tubercle*, 1948, **29**, 21.)

TABLE I.—DEATHS FROM ALL FORMS OF TUBERCULOSIS IN ENGLAND AND WALES (including in each case as a standard the figures for the last pre-war year.)

YEAR	ACTUAL DEATHS	YEAR	ACTUAL DEATHS
1913	49,476	1938	25,539
1916	53,858	1941	28,670
1917	55,934	1943	25,649
1918	58,073	1944	24,163
1919	46,312	1945	23,955

It is seen that the mortality rose and fell with the deterioration and improvement of the protein supply to a most faithful degree. The response of the tuberculous patient to changes in the fat content of his diet has been known for a long time but this very large experiment with the protein intake has shown the importance of animal protein to the tuberculous individual (Editorial, *Tubercle*, 1948).

Memories of the out-patient departments of the years before and during the 1914–18 war, and of the dirty, ill-nourished, ill-clad and often barefooted children who thronged the clinics, bring realization of the improvement that has taken place in the economic state of the mass of the population who constitute the majority of the hospital population. Their food, their clothing, their opportunity for leisure and entertainment have vastly improved but their housing remains a very urgent and serious problem. That patients suffering from open phthisis should be compelled to spend many months in the midst of their families—often of young children—in their overcrowded and often insanitary homes whilst waiting for a bed in a hospital or sanatorium is one of the greatest scandals of the present time and makes the improvement in the situation even more remarkable.

(Table I.) Inspection of the mortality figures for the period of World War I 1913–19 and for that of World War II 1938–45 (Report of the Chief Medical Officer, Ministry of Health, 1939–45, H.M. Stationery Office, London, 1946) shows that there was a steady increase in mortality from tuberculosis throughout the First World War, with a rapid drop immediately after the cessation of hostilities. In the second war it was only during 1940 and 1941 that there was an increase and by 1944, before the end of the war, the figures were improving, and continued to do so until 1947 when there was a slight rise—perhaps due to the difficult economic conditions and some temporary reduction in rations of that period. Consideration of the death-rates for the various age-groups, comparing those of 1939 with those of 1946, shows that for respiratory tuberculosis there has been a decrease for both males and females in all age-groups except those between 0–10 years, but that the greatest decrease has been in adolescents (the age-groups 10–20) and to a lesser extent between 20–25.

These matters are fully discussed in Dr. J. B. McDougall's book "Tuberculosis" (1949).

TABLE II.—DEATH-RATES FROM TUBERCULOSIS PER MILLION LIVING (INCLUDING NON-CIVILIAN AND BASED ON THE ESTIMATED TOTAL POPULATION AT RISK) IN 1946, COMPARED WITH 1939

	RESPIRATORY TUBERCULOSIS				OTHER FORMS OF TUBERCULOSIS			
	Males		Females		Males		Females	
Ages	1939	1946	1939	1946	1939	1946	1939	1946
0	54	68	38	60	408	308	354	263
5	15	22	20	24	143	107	115	124
10	31	22	86	68	87	97	97	88
15	368	240	601	475	144	110	117	112
20	682	497	955	856	116	84	90	102
25	723	619	707	667	84	59	68	61
35	859	679	469	380	72	58	42	40
45	1158	1002	352	259	68	63	39	29
55	1171	1144	300	37	71	46	28	36
65 and over	559	646	209	177	54	47	44	41
All ages (crude)	638	568	410	343	113	88	86	75

The period of greatest incidence of tuberculosis of the larynx is in young adults between 20 and 30 years, the decade 30–40 being the next—in the ordinary order of frequency. It is probable that many, if not most of the cases occurring between 20 and 30 years of age, have originally become infected in the years preceding that of 20 or even during the years 20–25—the periods of greatest decrease—and this change in the incidence is being reflected in the marked reduction in the number of cases developing tuberculosis in the upper air passages. The increase in the decades 0–10 is probably due to the infection by children of adults with active disease living at home whilst waiting for admission to an appropriate institution. Unless some great improvement is made in the accommodation of the tuberculous we may yet experience a rise in the number of cases of tuberculosis of the larynx.

The economic state of the patient must have a considerable effect on the problem but the facilities for earlier diagnosis which have resulted from the great improvement in the technique of radiography, by the introduction recently of mass radiography, and by the institution—earlier in the period under consideration—of tuberculosis medical officers and dispensaries by all local authorities must also have had considerable effect.

The improvements in treatment which have taken place during the past thirty years must also have played a part in these changes. In the period immediately after World War I, artificial pneumothorax was being used in a rapidly increasing number of cases and from personal observation had a very beneficial effect on an established tuberculosis of the throat

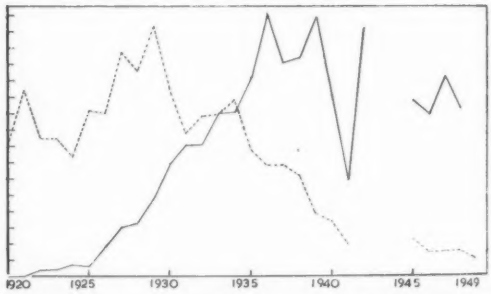
and therefore might be expected to have some part in its prevention. About this time operations on the phrenic nerve—to immobilize the diaphragm—were being introduced and being performed with increasing frequency. During this period, however, the incidence of tuberculosis of the larynx at the Brompton Hospital was increasing, in spite of these new methods of treatment. From 1925 the operations on the thoracic cage—thoracoplasty, thoracotomy with cutting of adhesions and various forms of apicolysis—were being developed, operations designed to give a more complete and permanent immobility of the lung. From 1930 onwards the surgery of immobilization made great progress. The technique improved, the mortality fell with the introduction of improved methods of anæsthesia, the results improved and the operations were carried out in much greater numbers in a rapidly increasing number of thoracic surgery centres. This coincides with the great fall in the number of cases of tuberculous disease of the upper respiratory passages and is probably one of the factors causing the decline. It is a matter of practical experience that successful immobilization of the lung by these means often results in improvement in a laryngeal or pharyngeal lesion, and again might be expected to prevent the occurrence of such a lesion in many cases.

Graph 5 gives the number of operations of immobilization—phrenic crushing and avulsion, thoracotomy, division of adhesions and thoracoplasty but excluding artificial pneumothorax and pneumoperitoneum — performed at the Brompton Hospital from 1920–49. A very steep rise occurred from the middle of the 1920s until saturation point appeared to be reached in 1937. The figures for the war period are unreliable as many of the patients were removed to hospitals outside London for their operations. The curve is seen to run in the opposite direction to that for the laryngeal lesions and this is well shown by superimposing the curve for the total cases of tuberculosis of the larynx on that for the total operations (Graph 6).

The last curve (dotted line) shows that as the operations of immobilization increased, the secondary lesions in the throat decreased, suggesting that the law of cause and effect may be involved.



GRAPH 5.— ——— number of operations for immobilizing lung. Brompton Hospital, 1920–49.



GRAPH 6.— ——— number of operations for immobilizing lung, ... number of cases of tuberculous laryngitis. Brompton Hospital, 1920–49.

During the period under consideration there had been no advances in the direct treatment of tuberculosis of the larnyx. Complete silence and application of the galvano-cautery were the only measures that had provided any real curative effects. There were a number of drugs and of therapeutic manœuvres that had great analgesic properties, but of the great variety of drugs, sprays, powders, paints, injections, of every type of irradiation and of other therapeutic applications, none had more than sporadic successes and none ever became established. Cures were obtained where the lungs were responding to treatment, but where the pulmonary condition was deteriorating or where it was active and stationary it was rare to make much impression. The advent of streptomycin has provided a means of relieving and frequently curing tuberculosis of the throat far superior to anything that had previously been available. Owing to the shortage of supplies in the early stages of its development and to the fact that its use was at first restricted to certain specific aspects of tuberculosis it was not until the latter half of 1948 that streptomycin became generally available for the treatment of throat conditions. A limited number of patients, who were able to obtain supplies from abroad, had been treated and the results had been uniformly good.

The antibiotic had been used in America for tuberculous laryngitis and very good results had been reported. It had been found in treating tuberculous pulmonary lesions that admini-

stration of 3 grammes a day was liable to damage both the cochlear and vestibular systems. 2 grammes a day damaged many vestibular systems but did not harm the cochlea. 1 gramme a day occasionally produced some transitory vertigo but no permanent bad effects. It was discovered that the administration of streptomycin might in a not inconsiderable number of cases lead to the appearance of a strain of tubercle bacilli which was resistant to the bacteriostatic effects of streptomycin. Fortunately it was also discovered that the addition of the sodium salt of para-aminosalicylic acid in doses of 15 to 20 grammes three times a day prevented the emergence of these resistant strains.

This is important because many of these patients are destined for surgery at a later date and it is essential that they should be susceptible to the good effects of streptomycin.

Larroude was one of the first to publish results and he had applied streptomycin as an aerosal spray, using 1 gramme of streptomycin in 20 c.c. of saline. He applied this three times a day to 12 patients and reported 1 cure, 8 very much better, the remainder either remained the same or deteriorated. Lieberman and Lell treated 37 cases by intramuscular injection and every one improved. O'Keefe used local applications as well as parenteral ones and reported good results. German and Mako used 1 gramme a day and stated that the greater proportion of the improvement occurred in the first three weeks and all of it in six weeks. William McKenzie reported 12 cases treated with 1 gramme a day at Milford Sanatorium. Of these 6 were cured, 5 much improved and 1 did not respond. Winn of the Springville Sanatorium in California in a personal communication states that acting on the advice of Bogen of the National Streptomycin Committee of America he now gives ½ gramme of streptomycin every seventy-two hours and 5 grammes of para-aminosalicylate of sodium three times a day for six months and had obtained very satisfactory results. It is the practice at Brompton that where the patient is living at home to send a supply of streptomycin and of distilled water and to ask the family doctor or the district nurse to give the daily injection.

Improvement begins early and is most dramatic in acute cases and especially where there is ulceration and pain on swallowing. The effect of streptomycin is to abolish the extremely severe pain in these cases in three or four days and the need for analgesics and injection or section of the sensory nerves of the larynx has almost disappeared. The sensitive part of a tuberculous ulcer is in the active part immediately under the undermined growing edge. Streptomycin acts most powerfully on active, spreading lesions and will have a very early effect on the growing, sensitive edge of the ulcer, thus allaying the pain and leading to healing of the ulcer. It has a slower but equally marked effect on œdema, and on granulo-tuberculomatous changes and on nodular infiltration. Its action is naturally least marked in old-standing lesions with fibrosis, in which irreversible changes have taken place. The majority of cases attain their maximum benefit after having received between 40 and 60 grammes, but others continue to improve up to 90 or a 100 grammes. In the most satisfactory cases the appearance of the larynx returns to normal, in others where there has been much swelling, especially of the ventricular bands and arytenoid processes, there will always be some residual thickening, though all active disease has disappeared. Movement and apposition of the vocal cords usually returns, unless ankylosis of the crico-arytenoid joints has occurred, and the voice is greatly improved or returns to normal. Even where much treatment has been carried out such as galvano-cautery, or surgical removal of tissue—in one case, of the whole epiglottis—the effect is not reduced.

The effect of streptomycin on the pulmonary disease is not so marked and it is now a frequent experience that the larynx heals and becomes normal while the lung steadily deteriorates. In a certain number of patients, however, the lungs do improve and even cavities become smaller. The results of the patients treated during the past eighteen months at the Brompton Chest Hospital and at the Midhurst and Milford Sanatoria have been taken together—the latter with the kind permission of Mr. William McKenzie.

The total number is 54 and Table III indicates the type of pulmonary disease which was associated. All but 7 had bilateral disease and nearly half had cavities.

TABLE III.—TUBERCULOUS LARYNGITIS
(54 Cases)

Treated with streptomycin	54	Cured	26	Died .. .. .. Total	6
Tubercle bacilli in sputum	47	Apparently cured but with		From extension of lung disease	2
Unilateral disease ..	7	some residual swelling ..	5	From genito-urinary disease	2
Bilateral disease	47	Great improvement ..	15	From tuberculous enteritis ..	1
Cavities	25	Slight improvement ..	3	Following thoracoplasty ..	1
		No change	3		
		Worse	2		

The results show that almost half returned to normal and 20 more became inactive. 6 patients have died and in 3 of these the larynx had returned to normal, 1 was improved and 2 had deteriorated.

The following 3 cases are recorded as examples. They each show very considerable improvement in the larynx, that of C. V. having eventually become normal. In R. T. and P. B. there were bacilli in the sputum and in C. V. a biopsy proved the tissue to be tuberculous. In R. T. there is perhaps some slight clearing in the lung field. In P. B. there is a cavity in the left lung which has decreased in size but otherwise the bilateral infiltration is unchanged. In C. V. if there is any change in the left upper zone it is for the worse but the difference in penetration may account for most of the change.

CASE I.—R. T., male, aged 38.

Infiltration of all zones of R. lung and upper and middle zones of L. lung. Tubercle bacilli present in sputum. October 6, 1945, seen at Brompton complaining of hoarseness and dysphagia. Ulceration on laryngeal aspect of free part of epiglottis. Tuberculous infiltration of posterior ends of both vocal

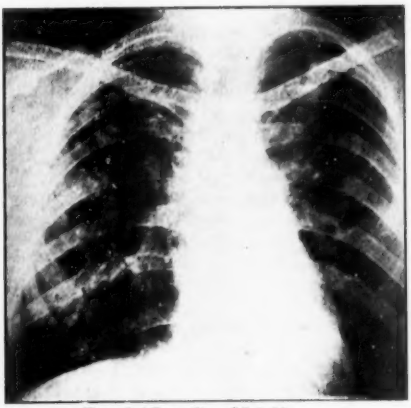


FIG. 1 (*Case I*).—25.1.49.



FIG. 2 (*Case I*).—1.10.49.

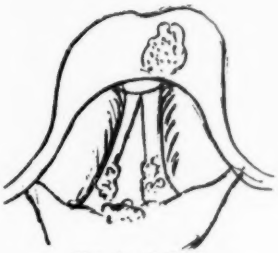


FIG. IA, 6.10.45.

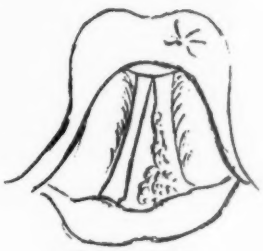


FIG. IB, 6.5.47.

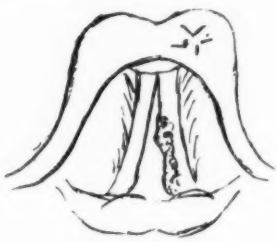


FIG. IC, 19.8.47.



FIG. ID, 18.1.49.



FIG. IE, 10.1.50.

cords and interarytenoid region with granulo-tuberculomatous formation. Silence, application of 25% argyrol, ulcer healed, infiltration cleared except at posterior end of L. vocal cord. Removed by forceps (May 1947). Later galvano-cautery applied. Early in 1948 infiltration spread to mid-point of L. vocal cord but remained quiescent. Except for hoarseness patient was quite well. January 1949 condition deteriorated rapidly. Ulcer reappeared on epiglottis. New one formed on L. arytenoid process and infiltration spread along whole length of L. vocal cord. Much pain and

hoarseness. General condition deteriorating. 50 grammes streptomycin with immediate response of larynx to normal within three to four months except for scar on epiglottis. During this period there was some slight clearing of the lung shadow.

CASE II.—P. B., male, aged 43.

Infiltration upper zones of both lungs with cavity on L. side. Tubercle bacilli in sputum. September 6, 1949, hoarseness and pain in throat. Nodular infiltration of epiglottis with ulcer in median line of laryngeal surface. Infiltration of R. vocal cord, both ventricular bands and R. arytenoid process. Fringe of tuberculous granulation tissue appearing from mouth of L. ventricle.



FIG. 3 (*Case II*).—4.10.49.



FIG. 4 (*Case II*).—25.4.50.

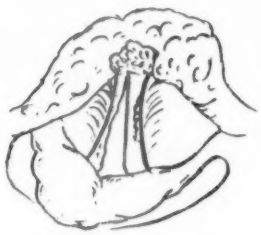


FIG. IIA (*Case II*).—4.10.49.

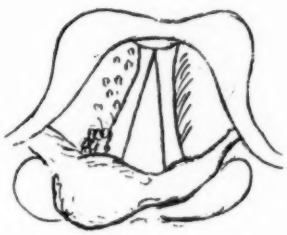


FIG. IIB (*Case II*).—22.11.49.

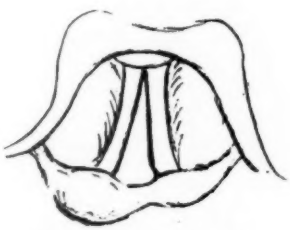


FIG. IIC (*Case II*).—4.3.50.

Streptomycin administered. After 49 grammes the epiglottis had returned to normal (November 22, 1949) and the infiltration had cleared from the cords. The R. ventricular band and arytenoid were still infiltrated and swollen. After 70 grammes the whole larynx had returned to normal except for some swelling of the R. arytenoid process which never cleared up. During this period the cavity in the left upper zone became smaller and there was some hardening at the R. apex.

CASE III.—C. V., female, aged 37.

Infiltration upper zone of left lung. Tubercle bacilli not found in sputum.

August 23, 1949. Complained of pain on swallowing especially on L. side for two months. Deep ulcer with much surrounding infiltration of pharyngeal aspect of L. aryepiglottic fold. Portion removed for biopsy—tuberculous tissue. Streptomycin administered. After 22 grammes all surrounding infiltration disappeared. Ulcer shallow. After 58 grammes only small knob of fibro-tuberculomatous tissue which later disappeared. Patient gained 21 lb. in weight.

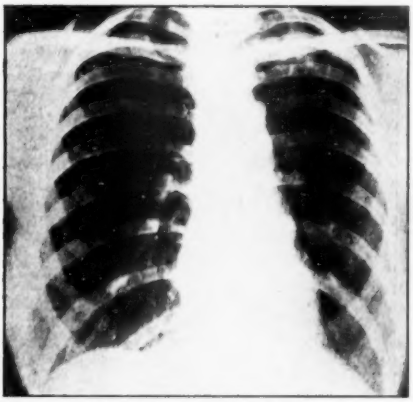


FIG. 5 (*Case III*).—30.8.49.



FIG. 6 (*Case III*).—28.3.50.

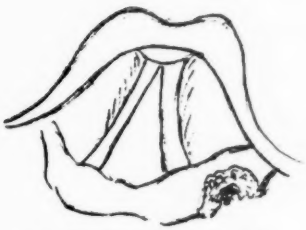


FIG. IIIA (*Case III*).—23.8.49.

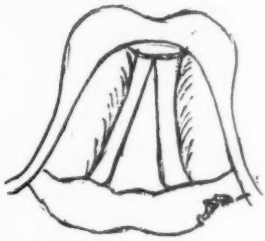


FIG. IIIB (*Case III*).—27.9.49.

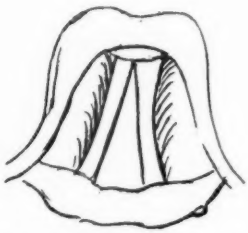


FIG. IIIC (*Case III*).—1.11.49.

During this period condition of left upper zone appeared to have deteriorated though his change may be exaggerated by variation in the penetration of the films.

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The Toxic Effect of Streptomycin on the VIII Cranial Nerve

By J. A. B. THOMAS, F.R.C.S.

BEGINNING in early 1947 streptomycin therapy was given to a group of patients suffering from pulmonary tuberculosis at Brompton Hospital, London.

The clinical observation of the chest condition was undertaken by Dr. John Crofton and Dr. J. R. Bignall. The Ear and Throat Department under Professor Ormerod undertook the investigation into any VIII nerve toxicity which might arise. In this Drs. Crofton and Bignall were of great assistance, in that they made an almost daily search for nystagmus and vertigo.

As many patients as possible were examined at the Ear and Throat Department before streptomycin treatment commenced or within the first fortnight of therapy. During treatment they were examined at monthly intervals while a final examination was made after cessation of streptomycin therapy. Every patient was given a full routine E.N.T. examination including caloric vestibular reactions and a note was made of the upper tone limit registered on the monochord. The galvanic test was carried out when the caloric reactions could not be elicited.

Caloric tests were performed in the manner laid down by Cawthorne, Fitzgerald and Hallpike, using water at 30° and at 44° C., the only modifications being that the patients sat in a dental chair which could be tilted to the required degree and the douche can was placed on a convenient dental arm 18 in. above the meatus.

The galvanic test was performed by placing a flat metal electrode covered with four to six layers of lint soaked in saline over the mastoid region. This was held in place by a bandage surrounding the head. A wooden or metal rod was placed in the bandage at the forehead and used as an indicator. The indifferent electrode was held in the hand. The current was gradually increased from zero to about 4 to 8 ma. when the sensitivity of the nerve elements was indicated by a lateral inclination of the head towards the anode or away from the cathode. It would be necessary to increase the current much above this level to elicit nystagmus and so cause a considerable degree of pain.

The symptoms and signs of toxicity especially looked for in our investigation were vertigo, spontaneous nystagmus, past-pointing, and changes in caloric and galvanic reactions.

Vertigo.—A total of 76 patients were seen, of whom 10 were treated by intermittent dosage of 2 grammes in alternate weeks or months.

Of 66 treated continuously 21 had giddiness divided as follows:

TABLE I

	Total	Vertigo
Those having 2 grammes divided dose per day ..	23	14
1 gramme 2 doses per day.. ..	13	4
1 gramme single dose per day ..	30	3

On comparing the 2 grammes and 1 gramme in day groups it is evident that patients receiving 2 grammes per day were almost four times more likely to become giddy than those on 1 gramme a day.

The giddiness was present continuously and very severely in 2 patients, both of whom were over 45 years of age and both were members of the medical profession.

In the others the vertigo was complained of after sudden movements such as turning in bed when they felt as if they continued to turn, or on sitting up in bed they felt the process continuing. This usually disappeared in a minute or so.

No past-pointing was noted in any of these patients complaining of giddiness with or without nystagmus.

In those with slight giddiness the symptoms lasted less than four weeks, while those with more severe vertigo it lasted longer than four weeks. Thus, if the giddiness experienced is slight in amount, recovery in a short time can be expected, whilst if severe giddiness occurs there may be considerable delay in recovery.

Time of onset of vertigo.—In 16 cases having 2 grammes daily, the mean day of onset of vertigo was the twenty-second with a standard deviation of seven days either way.

With 1 gramme daily (7 cases) the mean day of onset was the forty-fifth, with a much wider standard deviation of twenty-four days. This wide deviation is probably due to the small numbers employed, even so the difference observed is statistically significant.

Nausea was less frequently experienced on the 1 gramme a day group than on those taking 2 grammes daily, but the time of onset of the nausea does not show the same relationship to the size of the dose as does giddiness.

Nystagmus.—In 21 patients a first degree spontaneous nystagmus was seen, i.e. nystagmus occurred on looking laterally. In the majority of cases it was present on looking to the right and to the left. This suggests a bilateral stimulation of the vestibulo-oculomotor pathway.

TABLE II

Of 22 cases having 2 grammes per day continuously, 14 had nystagmus.
Of 43 cases having 1 gramme continuously only 7 had nystagmus.
Thus, nystagmus occurs four times as frequently in the 2 gramme group as in the 1 gramme.

Relationship to giddiness.—Of 23 patients who complained of giddiness at some time, nystagmus was detected in 17 at some point during the period of observation.

Of 51 who experienced no giddiness, 8 had nystagmus.

Time of onset.—There was no difference in the time of onset of nystagmus in the two dosage groups but 13 out of 21 showed nystagmus during the first month.

Another ocular manifestation of toxicity was the inability to focus the eyes quickly on to a distant object after looking at a near one. For a short time the distant object appeared to shimmer or vibrate. This is probably due to a very fine nystagmus on attempting to accommodate.

Caloric tests.—In many cases it was impossible to obtain a month by month picture of the changes in the caloric reactions particularly in the 1 gramme group. In some cases the patients were too ill, were transferred to sanatoria or underwent surgical operations. However, where possible an assessment of the change in caloric responses was made at the end of the third month and after completion of treatment, which in every case exceeded four months.

The following figures give some idea of the changes which take place in the caloric reactions:

TABLE III

Group A received 2 grammes per day continuously

	At the third month	Final assessment
Impossible to assess	5	3
Caloric reactions:		
Remain unchanged ..	9	6
Become reduced	2	6
Reactions disappeared ..	6	7
	22	22

TABLE IV

Group B received 1 gramme a day

Impossible to assess	10	11
Caloric reactions:		
Unchanged	5	1
Reduced	1	1
Disappeared	1	4
	17	17

Group C consisted of 10 patients receiving 2 grammes per day intermittently on alternate weeks or months, in an attempt to delay the development of a streptomycin resistance. It was impossible to assess 6 of these but in 2 cases the caloric reactions remained unchanged and in 2 they became absent.

The paucity of numbers in the 1 gramme per day group makes it difficult to draw any definite conclusions, but it appears that 1 gramme per day given over a prolonged period (up to eight months) is quite as liable to produce definite vestibular disturbance as 2 grammes per day given for a shorter period.

Our final assessment gives 13 patients who had absent caloric reactions to water at 30° and 44° for 40 seconds, and to water at 21° for 1 minute.

In cases showing vestibular disturbance the absence of response to hot caloric stimulation was the earliest and most frequent change detected. Directional preponderance occurred less frequently while occasionally a canal paresis became manifest.

The pattern changes are not stressed because of the difficulty in deciding in many cases the end-point of the nystagmus.

The galvanic test was performed when the caloric reactions became absent to water at 30° and 44° and to water at 21° for 1 minute. In the 13 cases which gave no caloric reactions the galvanic test was found to be positive in each case. This suggests that some abnormality has occurred in the end organ leaving the vestibular nerve capable of stimulation.

Hearing.—None of our patients complained of any hearing loss or of tinnitus. Their upper tone limits, as tested on the monochord, remained unchanged throughout treatment.

Discussion has centred around the site of the lesion and whether there is any possibility of recovery from the vestibular damage caused.

Compensation occurs readily in young subjects. Our patients had an average age of 25 years.

Unsteadiness is felt only when walking in total darkness or with the eyes shut. Patients with less complete compensation have difficulty in performing sudden changes of posture.

It was possible to re-examine 8 patients twelve months or more after cessation of streptomycin therapy. All these had previously lost their caloric reactions to water at 30°, 44° and 21° for one minute. In 3 of these cases there was no evidence of recovery but in 2 of these galvanic stimulation produced no response. In 4 cases it was possible to obtain a reaction to the test with water at 21° for 1 minute.

One patient who complained of vertigo but no nystagmoid response to cold 21° caloric stimulation in October 1948, on retesting three months later gave a response to water at 30° and 44°. This was two months after cessation of streptomycin. On retesting seventeen months later she gave normal caloric responses.

These cases show that some recovery is possible after severe depression of labyrinthine function.

Site of lesion.—No definite conclusion has yet been reached on this point.

Clinically the signs and symptoms are not typical of either a peripheral or of a central lesion. Histological changes have been shown to occur in the medial longitudinal bundle, in Deiter's nucleus and in the cupolæ of the semicircular canals. Such evidence is mainly based on experimental studies in animals given large doses of streptomycin.

Further pathological evidence on the human labyrinth is needed before a definite statement can be given.

Miss M. R. Dix said that about a year ago Mr. Hallpike, Mr. Harrison and herself had had the opportunity of carrying out the galvanic test at Queen Square on a number of streptomycin-treated patients, with very different results (*Brain* (1949) **72**, 241).

The point of their enquiry was rather a different one. They were interested in Ohm's theory that optokinetic nystagmus and vestibular nystagmus both depended upon the vestibular nuclei. Now the bulk of the published evidence available showed that streptomycin exerted its toxic effect upon the vestibular system, including abolition of the caloric responses, by destroying the vestibular nuclei. In their cases the caloric responses were certainly found to be grossly reduced, but the optokinetic responses were quite normal.

From this they argued that optokinetic nystagmus does not depend upon the vestibular nuclei. But, in addition, considerable reduction in the galvanic responses was found. This accorded with the general notion of a lesion of the vestibular nuclei but it was contrary to and not in accordance with Mr. Thomas' findings.

It was realized that the technique by which this test was done had a large bearing on the results obtained.

H. C. Purcer Smith said that an interesting point in his series was that in 6 cases during the two, three or four days before the onset of vestibular loss one got hypersensitivity indicated by caloric response. The bed-fast patients stood tests very well without undue subjective reaction. The tests were performed according to a standardized and reliable technique using cool air. In his series it was rare to find the hearing affected by chemotherapy except for one or two cases of high tone loss in young children. The monochord was an excellent instrument where the detection of high tone loss in these young people was important. The preliminary hypersensitivity before the onset of the vestibular palsy pointed to a central loss,[1] and the impression gained from labyrinth tests at the Manchester Royal Infirmary was that the pathological changes occurred centrally and not in the end organ.

J. A. B. Thoma in reply: It is suggested by the 2 cases examined twelve months after cessation of streptomycin therapy, that the absence of response to galvanic stimulation is a much later phenomenon than the loss of caloric reaction.

The Clinical Aspects of the Streptomycin Treatment of Pulmonary Tuberculosis

By J. R. BIGNALL, M.A., M.D., M.R.C.P.
Institute of Diseases of the Chest, Brompton Hospital

THE treatment of pulmonary tuberculosis with streptomycin is dominated by the phenomenon of bacterial resistance. The ease with which resistant strains of tubercle bacilli emerge during prolonged treatment has considerably reduced the therapeutic effect of the antibiotic and prevented its wider use.

It has been discovered that the process of the replacement of streptomycin sensitive by resistant bacilli can be to a large extent prevented by treating the patient simultaneously

[1]The dissociation from hearing loss again pointed to central loss.

with para-aminosalicylic acid (P.A.S.) and streptomycin (M.R.C., 1950*c*). This has been a major advance, but the problems of bacterial resistance have certainly not been solved. Streptomycin resistance still appears in a small proportion of cases treated with 1 gramme of streptomycin and 20 grammes of sodium P.A.S. daily. It is so far not known whether even this partial protection can be obtained when smaller doses of P.A.S. are used.

Investigation of bacterial resistance has been frequently very much neglected. Although P.A.S. was first used in human pulmonary tuberculosis in 1946 it was not until quite recently that the development of P.A.S. resistant bacilli during treatment was observed (Delaude *et al.*, 1949). Even now very little is known about it although P.A.S. is being very widely used in many types of tuberculous disease.

Studies in resistance development have, of necessity, to be carried out on patients who continue to excrete bacilli in the sputum. These studies have shown that resistant bacilli are more likely to appear in the sputum of those with pulmonary cavities and massive areas of tuberculous pneumonia. Very little information is available about the streptomycin sensitivity of the bacilli remaining in the patients' tissues after they have disappeared from the sputum during streptomycin treatment.

Until more is known about the development of bacterial resistance during treatment with combinations of drugs, particularly in the less severe types of pulmonary disease, the indiscriminate use of streptomycin and para-aminosalicylic acid should be discouraged.

Toxicity.—Toxic effects of the combined treatment are not negligible. The vestibular disturbances are well known. Rashes and drug fever due either to streptomycin or P.A.S. occur infrequently. Acute febrile reactions due to P.A.S. are, in general, more common and more severe than those due to streptomycin. It is usually possible to desensitize the patient by the usual method of small ascending doses until the full daily dose has again been reached. About half the patients treated with 20 grammes sodium P.A.S. daily complain of nausea, vomiting or diarrhœa, and rather more have slight dyspeptic symptoms and depression of appetite.

Dermatitis in nurses handling streptomycin is not common but it is important when there is a shortage of nurses for tuberculous patients. The wearing of rubber gloves during handling of the containers and syringes is an effective prophylactic measure.

Effect on the patient.—Even in patients whose pulmonary disease appears to show no radiological alteration during treatment a reduction or abolition of fever, gain in weight and increase in the feeling of well-being very commonly occur when streptomycin is given. This effect of streptomycin is frequently dramatic and it has been said that if no improvement in the patient is detected after a month, none is likely to occur and the drug might as well be stopped. This is a generalization to which there are, of course, exceptions; but if it were borne in mind it might prevent needless continuation of an expensive treatment in patients who, by the very nature of their disease, are incapable of gaining any lasting benefit.

Effect on the lung disease.—Three pathological types of pulmonary tuberculosis, miliary tuberculosis (M.R.C., 1950*a*), tuberculous pneumonia (M.R.C., 1948) and tuberculosis of the bronchial mucous membrane (M.R.C., 1950*b*; Brewer and Bogen, 1947), show an unequivocal response to streptomycin which has been demonstrated by carefully conducted clinical trials. The response of all other varieties of pulmonary tuberculosis is not accurately known. Streptomycin has been employed, without doubt, in every type of tuberculous lung disease but the results are very difficult to assess without planned clinical experiments. It is, for instance, being used to prepare patients for collapse therapy, prophylactically during the early stages of artificial pneumothorax treatment, in tuberculous pleural effusions and in " minimal " tuberculosis, or non-cavitated disease of limited extent. It will be necessary to wait many years before the accumulated individual experiences of such treatment have crystallized into generally accepted views.

The response of miliary tuberculosis is well known. The clearing of the radiographic shadows may be dramatic and the late results seem to be encouraging. 56% of the M.R.C. series have survived for longer than two years (M.R.C., 1950*a*).

The lung lesions in most cases of so-called "acute tuberculous bronchopneumonia" are not purely pneumonic. The pneumonia has usually originated from chronic cavities in older, fibrotic areas by the dissemination of infected material through the bronchial tree. Streptomycin is capable of directly altering the pneumonic lesions; but any slight effect on the chronic disease and the old cavities is probably mainly secondary to improvement in the patient's general condition and in the tuberculous lesions of the small bronchi, which are an invariable accompaniment of chronic lung cavities. Chronic cavities only rarely close with streptomycin and bed rest alone. Commonly the usual collapse measures or pulmonary resection are necessary to deal with the residual chronic disease.

The response to chemotherapy can never be accurately predicted, least of all by mere inspection of the chest radiograph. It is the patient who heals the disease, not the streptomycin. If the innate ability to destroy the infecting organisms and heal the damaged tissues is inadequate, chemotherapy can do little.

Other chemotherapeutic substances.—At present streptomycin is the most effective drug against human tuberculosis that is known. The main use of P.A.S. is in conjunction with streptomycin. Only in certain special circumstances does it seem justifiable to use P.A.S. alone. The sulphones have not proved to be of much value so far. The German drug thiosemicarbazone has been extensively used on the Continent. It is difficult to judge the results in pulmonary tuberculosis. In laryngeal tuberculosis it appears to be quite active and it may possibly prove to be of value in the treatment of this condition. The possible development of bacterial resistance to the sulphones and thiosemicarbazone has not been adequately investigated. Many thousands of patients in Germany have received thiosemicarbazone but only in the last few months has the development of bacterial resistance to the drug been recorded (Davis and Schwartz, 1950). It is not known whether combinations of either drug with streptomycin will prevent the development of streptomycin resistance. Until these fundamental bacteriological studies have been done I doubt whether the use of these drugs, other than experimentally, is justified.

The ultimate object of the chemotherapy of pulmonary tuberculosis is not the treatment of far-advanced disease or preparation of the patient for pulmonary resection, artificial pneumothorax or thoracoplasty; it is the eradication of the disease at the earliest stage at which it can be diagnosed. This goal is still very far away.

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Electro-Encephalography in Relation to Otorhinolaryngology

By J. D. SPILLANE, M.D.

THE electrical activity in the peripheral nervous system is very much simpler than that of the brain. In addition to the ordinary action potentials that accompany the transmission of a nervous impulse, there is, in the brain, continuous rhythmic oscillatory variations of potential difference. An electro-encephalograph is a sample of this activity: many processes contribute to the whole pattern of the graph. The normal dominant pattern (the alpha rhythm) of the adult brain at a frequency of about 10 cycles per second may be disturbed by a variety of lesions. The resulting abnormal records may be similar in several respects although the processes that provoke them are quite distinct. Thus, diffuse symmetrically distributed slow waves (at 2 to 4 c/sec. delta waves) may result from raised intracranial pressure (from any cause) or from basal meningitis; again, an area of "electrical silence" over the temporal lobe might occur in meningioma, subdural hæmatoma or extradural abscess. A focus of abnormality in one hemisphere indicating an intracerebral space-occupying lesion may be due to the presence of tumour, abscess, cyst or hæmatoma.

Cerebral abscess.—Although advances in antibacterial therapy have reduced the incidence and mortality rate of otogenic cerebral abscess and made operative treatment less dangerous, it must be admitted that it has also made cerebral abscess a more difficult lesion to detect. The symptoms of invasion of the brain after adequate aural drainage has been established, i.e. malaise, anorexia, fever, tachycardia and headache may be entirely absent. The development of focal symptoms and signs—hemiparesis, aphasia or epileptic disturbance—may be the first indication that a cerebral lesion has developed. The control of fever, meningitis and of cerebrospinal fluid reactions and the reduction of septic absorption are among the beneficial effects of modern antibacterial therapy which, while reducing the likelihood of infection of the brain itself, also mask the signs of invasion when it does occur. Antibacterial therapy retards the development of inflammatory œdema in cerebral tissue so that headache, drowsiness, papillœdema and raised intracranial pressure may be relatively slight. This is especially significant when we are dealing with abscess in the cerebellum.

What help can we expect from the electroencephalograph? Lesions in the posterior fossa are not accompanied by any specific pattern or distribution of abnormality. Certainly, foci of delta activity are usually lacking. But the presence of internal hydrocephalus may be suggested by a diffuse distribution of theta rhythm (4–7 c/sec.). In Fig. 1 is illustrated the tracing from a patient with otogenic meningitis and a cerebellar abscess in whom there were flat optic discs and normal lumbar cerebrospinal fluid pressure. The E.E.G., taken when the clinical and C.S.F. signs of meningitis had subsided, showed that, despite these findings, the presence of diffuse high potential theta activity at 5 c/sec. in all leads with scattered delta activity (1½ c/sec.) pointed to a C.S.F. block.

Abscess in a cerebral hemisphere may be identified and located by a focus of delta activity. Although not differing essentially from tumour in electrical behaviour, in cerebral abscess the delta waves are often slower, more irregular and of higher voltage. The presence of surrounding œdema may mask the focal origin of the delta waves but with chronic encapsulation the slow waves may gradually reveal themselves as sharply focal. The principle of location of a space-occupying lesion by E.E.G. (i.e. finding the source of the slow waves) entails the identification of a point on the scalp at which apparent reversal of phase of the significant waves occurs. This method is illustrated in Fig. 2. When four electrodes are placed in a line over a hemisphere showing abnormal activity and connected to three independent recording systems any potential difference, for example, near the third electrode, will result in a phase reversal between amplifiers 2 and 3.

Phase reversal as a method of localization of a cerebral abscess is illustrated in Fig. 3. Here we see very slow irregular waves of high voltage in leads 5 and 6. Phase reversal in these leads led to correct localization in the left temporal region of an otogenic cerebral abscess.

Meningitis is often accompanied by the appearance of diffuse slow waves which cannot be differentiated from those associated with raised intracranial pressure. Serial records in a case of otogenic meningitis would be valuable in the event of localized abscess formation. The apparent quiescence of such cases should be doubted when one or more foci of slow waves gradually emerge in the E.E.G.

In 2 cases of *otitic hydrocephalus* the E.E.G was within normal limits. The raised pressure within the ventricular system in this condition may at times be associated with temporary slowing of rhythm.

Acoustic neuroma.—As already stated, lesions in the posterior fossa do not often produce E.E.G. abnormalities other than those which result from raised intracranial pressure. Cobb (1950) has found that auditory nerve tumours "show more normal records than any other anatomical grouping: the greatest abnormality is likely to be in the ipsilateral temporo-occipital region".

Figs. 4A and 4B are tracings obtained from 2 patients with auditory nerve tumours. In Fig. 4A there is high potential theta and delta activity in all leads. The patient had very high C.S.F. pressure with papillœdema and displacement of the brain-stem. He died after operation. In fig. 4B the tracing is nearly normal. There was no papillœdema and cerebrospinal fluid pressure was 190 mm. The tumour was successfully extirpated. The possible prognostic significance of such E.E.G. abnormality might therefore be studied in other cases.

Falling episodes in late adult life (epilepsy and vertigo).—A not uncommon clinical problem is that of the differential diagnosis in a case where sudden falling attacks, without warning or apparent loss of consciousness or convulsions, are the complaint. Not infrequently the patient is middle-aged and in otherwise good health. There is no family history of epilepsy and clinical examination of the cardiovascular and nervous systems throws no light on the origin of the episodes. The patient recounts how, at infrequent intervals, he unexpectedly falls to the ground, usually in a forward direction; sometimes he cracks his knees on the pavement and seeks treatment at an orthopædic centre for a fractured patella. This injury may occur on more than one occasion. He is able to get up immediately and walk away—sometimes after looking around as if he expected to find some obstacle over which he had stumbled. In the majority of instances the patient believes he was not unconscious and yet he may not be able to recall the moment when he was actually falling. He usually reassures those who run to help him to his feet, and mutters that he is quite all right and able to proceed. This he does. Such "drop seizures" or "static seizures" were described by Ramsay Hunt (1922) as a variety of epilepsy. Certainly such attacks may occur in epileptic subjects but when they make their appearance in late adult life, epilepsy may not at first come to mind.

Now, although the common vertiginous episodes that characterize Ménière's syndrome can usually be readily distinguished from "drop seizures" we must all have encountered cases in which it is difficult to decide whether the falling attacks are of cerebral or labyrinthine origin. Patients who suffer from the classical Ménière's syndrome may at times fall abruptly to the ground. There is no giddiness or warning in these so-called otolithic attacks which may precede the development of vertigo so that for some time their true nature may not be determined. I have had the experience, as I am sure others have also had, of dealing with middle-aged patients in whom middle-ear deafness co-existed with a history of falling episodes which were ultimately proved to be epileptic. Epilepsy of late onset is not uncommon and not infrequently it exhibits the characteristics of "drop seizures". It is not surprising that periodically one meets with such patients who have some degree of deafness.

In the elucidation of these cases I do not think anything will replace the meticulous taking of the clinical history but the E.E.G. may offer assistance of a positive kind. Labyrinthine disease does not alter the E.E.G., while minor epilepsy, of which "drop seizures" may be a

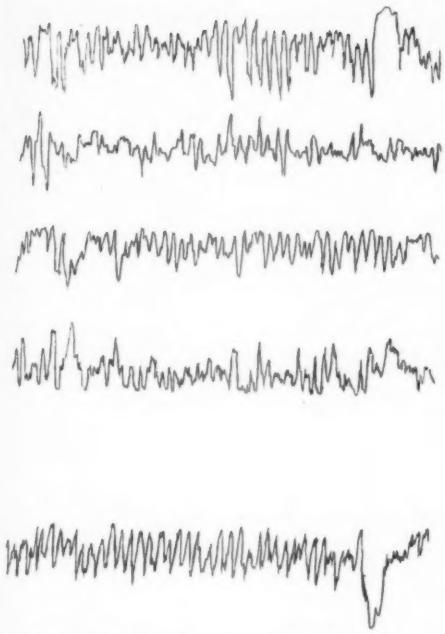


FIG. 1.—Otogenic cerebellar abscess with meningitis. Diffuse high voltage 5/sec. waves and scattered 1½/sec. waves.

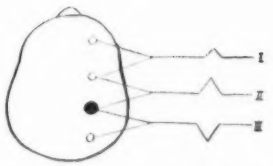


FIG. 2.—Localization by phase reversals.

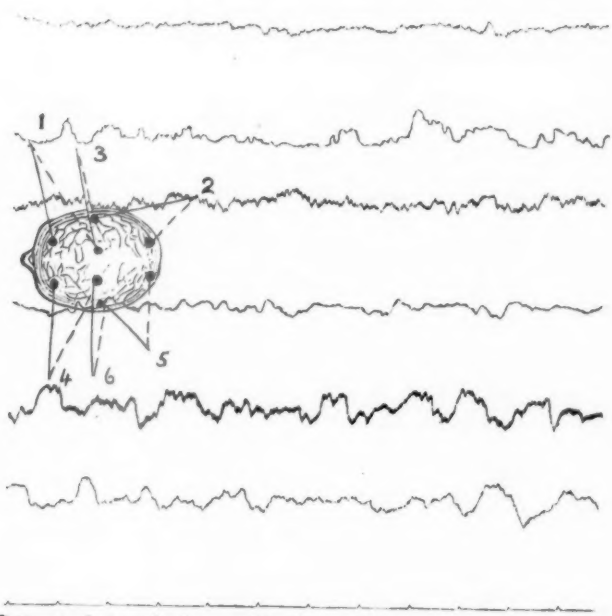


FIG. 3.—Left temporal otogenic abscess. Slow irregular waves of high voltage in leads 5 and 6.

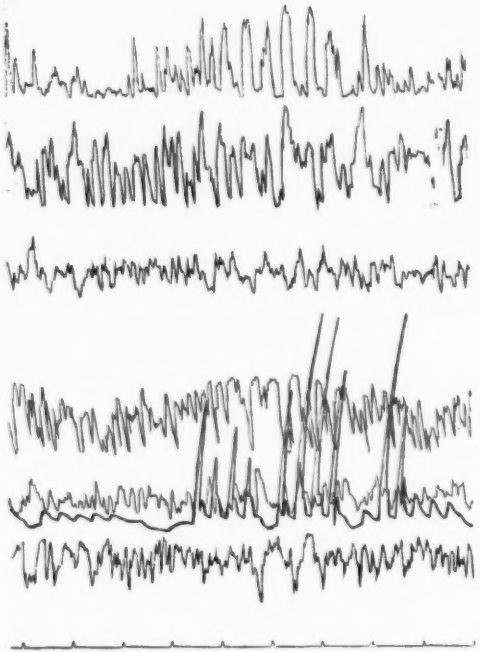


FIG. 4A.—Acoustic neuroma with high intracranial pressure showing high voltage theta and delta activity in all leads.

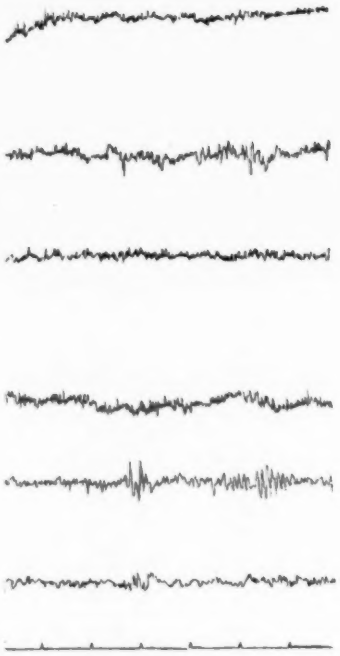


FIG. 4B. — Acoustic neuroma with normal intracranial pressure. Slightly abnormal record.



FIG. 5.—Female, aged 53. Chronic otitis media and "drop seizures". Single wave and spike discharge of *petit mal*.

manifestation, tends to reveal itself in the wave and spike pattern of the E.E.G. Unfortunately this pattern of E.E.G. abnormality, pathognomonic of epilepsy, is uncommon in epileptics over 40 years of age. General dysrhythmia is then more likely to be observed. Here are two illustrative cases.

CASE I.—Female, aged 53, typical "drop seizures" for eighteen months, eight or nine in all. No abnormality of the nervous system on clinical examination. Chronic otitis media (R.) with moderate deafness and slight tinnitus. E.E.G. (Fig. 5) revealed a single burst of characteristic wave and spike activity in all leads, indicating epilepsy. No evidence of progression of deafness or tinnitus during a two-year period of observation. One attack only during past eight months while taking Tridione 0·3 gramme twice daily.

CASE II.—Female, aged 55, with attacks of "giddiness" for two years. An attack consists of sudden unsteadiness and a sensation of the ground tilting up to the right. Usually falls if she cannot sit down immediately. Vomited in two attacks. Has had about thirteen attacks in all. No loss of consciousness until last episode, when she was thrown violently to the ground as she made for her couch. She had been treated as a case of Ménière's syndrome but there had been no development of deafness. Occasionally she has had bouts of tinnitus and in her last attack tinnitus persisted for several hours. E.E.G. showed periodic fast activity. Hyperventilation increased the dysrhythmia and produced two short bursts of epileptic activity. The patient married one year later and her husband recently informed me that on at least two occasions she has had an epileptic convulsion in her sleep.

"*Laryngeal Epilepsy.*"—The affection termed "laryngeal vertigo" by Charcot in 1876 and sometimes referred to as "laryngeal epilepsy" is one in which loss of consciousness follows a bout of coughing. It is usually met with in obese middle-aged men suffering from chronic bronchitis with emphysema. The suddenness of the episodes, the loss of consciousness, falling, and transient convulsive phenomena that may occur have long been taken to indicate that a cerebral disturbance of an epileptic character must take place. The condition is not a rare one and in a recent comprehensive examination of the problem Baker (1949) concludes that its epileptic nature is unproved. Baker argues convincingly that the loss of consciousness is the result of the prolonged increased intrathoracic pressure due to violent coughing against a closed glottis. Diminished venous return to the right heart leads ultimately to defective systemic circulation and cerebral anoxæmia. He suggests that the noncommittal title of the Cough Syndrome be applied to this malady.

Certainly, the evidence for epilepsy in such cases has never been strong and reflex cerebral inhibition from the larynx has rarely been demonstrated. But, as Baker points out, abrupt unconsciousness after only a *slight* cough, which I have witnessed, makes the reflex hypothesis not unlikely in some cases. I have satisfied myself that there are instances of sudden transient unconsciousness which result from a reflex effect from the pharynx, larynx or œsophagus and that the elaborate circulatory disturbances arising from prolonged coughing cannot explain all cases of so-called laryngeal epilepsy. That term could still be applied to cases such as the following:

CASE I.—Male, aged 47, trawler skipper. Decorated during the recent war. Since the age of 36 he has been subject to attacks of sudden loss of consciousness while eating or drinking. He has had about fifty attacks and every single attack has occurred while swallowing solids or fluids. He falls abruptly to the ground in nearly all of them and has sometimes injured himself. Recovery is immediate. He is unconscious for probably ten seconds. Rarely the sudden unconsciousness is replaced by a tickling, choking sensation in his throat and a feeling of faintness. Repeated and detailed investigations have disclosed no abnormality. I have never been able to stage an attack and no circulatory, electrocardiographic or electroencephalographic changes were obtained by breath-holding, swallowing, coughing, hyperventilation, carotid pressure, or tickling the throat. Coughing is in no way related to this syndrome.

CASE II.—Male, aged 55, chronic bronchitis and emphysema. For the past year he has had attacks in which he abruptly falls to the ground in an unconscious state and he has injured himself on several occasions. Recovery is rapid (10–60 seconds) and there are no after-effects. The majority of his attacks follow a bout of hard coughing which distresses him. *But at other times he feels merely a tickle in the throat, coughs once or twice, and becomes unconscious.* I watched one such episode. He put his hand to his throat, gave one short cough as if to clear his throat, and fell from his seat unconscious. In other attacks he has been stricken at the table during a meal. A bolus of food sticks in his throat, he tries to clear it but falls unconscious.

Cough may at times be minimal and the rapid sequence of the whole episode does not suggest that the "building up" as it were of the chain of circulatory events described by Baker can be the only explanation.

The electroencephalograms in these and other similar cases have been normal. It would be helpful to know whether a paroxysmal cerebral dysrhythmia can be provoked by some form of laryngeal stimulation. But I mention the subject only to illustrate the limitations of the application of the E.E.G.

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Section of Otology with Section of Laryngology

SUMMER MEETING HELD AT CARDIFF

OTOLOGICAL SESSION

[*June* 30, 1950]

Chairman—GAVIN YOUNG, M.C., M.B., F.R.F.P.S.Glas.
(President of the Section of Otology)

The Difference Limen of Intensity Variations of Pure Tones and its Diagnostic Significance

By Professor E. LÜSCHER

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ON the analogy of the classical hearing tests by means of tuning-forks and monochord, audiometry was limited primarily to the determination of the threshold values of pure tones. Audiometry proved to be a superior quantitative measuring method but threshold audiometry could not surpass the results of the usual hearing tests, mainly because, like these, it determined only the threshold values of the different frequencies by air and bone conduction. For some considerable time, but particularly during the last few years, entirely new methods have been introduced; principally the examination of tone intensities above threshold, which was not possible with the tuning-fork because of fading. In addition to the recruitment phenomenon and closely related to it, the difference limen of tone intensity variations is now of particular interest.

The determination of the recruitment phenomenon is only easy in monaural deafness, i.e. if the diseased ear may be compared with the normal ear by the "loudness balance", it becomes difficult in binaural deafness, especially in cases where the hearing loss curve runs more or less horizontally. On the other hand the determination of the difference limen is a monaural method, which may be applied in any form of deafness with the same ease.

The first to try to evaluate the difference limen diagnostically was Brinitzer in 1935, but his apparatus was inadequate; after him Göran de Maré in 1939 mentioned it, but only v. Békésy reached practical results in 1947 (*a*), at the same time we (Lüscher and Zwislocki, 1948*a* and *b*) began our investigations independently. Since then several further papers have been published—1947 (*b*): v. Békésy; 1948: Holmgren; 1949 (*a* and *b*): Lüscher and Zwislocki, Lüscher, Langenbeck, Denes and Naunton, Halm; 1950: Lüscher and Ermanni, Stoecklin and others.

The following paper is the outcome of collaboration with my physicist and Head of the Acoustics Laboratory, Dr. J. Zwislocki, several of my assistants and of my audiometry assistant Miss Gysin. J. Zwislocki constructed the audiometers used and checked their accuracy during our investigations.

DEFINITION OF THE DIFFERENCE LIMEN

The difference limen for tone intensity variations is the smallest change of tone intensity ($\triangle$ I), i.e. the smallest variation of the sound pressure ($\triangle$ p), which is just perceived as a variation of the (subjective) loudness. This is the absolute difference limen. If it is related to the adjusted intensity or pressure of the tone, the relative difference limen is given by the formula

$$\frac{\triangle I}{I} \quad \text{or} \quad \frac{\triangle p}{p} \quad \text{respectively. (Fig. 1.)}$$

It may be expressed either in per cent or in decibels; we prefer the former which is a linear function and therefore clearer. The relation between per cent and decibels is given in Table I.

TABLE I.—RELATION BETWEEN PER CENT OF THE SOUND-PRESSURE AND DECIBELS

%		db.
50	=	6·02
20	=	1·94
10	=	0·92
6	=	0·54
2	=	0·18

As the difference limen amounts normally to 10 to 16% under the conditions of our investigations and is even smaller in cases of deafness, the variations are mostly smaller than two decibels.

Determination of the Difference Limen

G. v. Békésy (1947*a*) uses a half-automatic audiometer constructed by himself to determine the difference limen. The driving motor varies the frequency continuously as the test proceeds so that the whole frequency band of the apparatus from the lowest to the highest frequencies is run through in about twenty minutes. The patient presses on a button thereby increasing the tone intensity and he keeps on pressing until he hears the tone, then he releases the button thus producing a continuous decrease of the tone intensity.

As soon as the patient no longer hears the tone, he presses the button once more till the tone appears again. In this way, the patient determines the whole audiogram himself. The audiogram appears as a jagged line round the threshold value. The variations amount to 15 to 20 db. in normal hearing. In conduction deafness the extent of the variations remains normal, in perception deafness the variations are considerably smaller. This means a diminution of the difference limen as a result of the recruitment phenomenon.

Not the whole of the variation determined by the method of v. Békésy can be ascribed to the difference limen, as the difference limen amounts to only 2 to 6 decibels at the threshold according to Riesz (1928, 1933) and the investigations of Neuberger (1950). A considerable part must be ascribed to the reaction time of the patient, his concentration and possibly to fatigue. For this reason the intensity variations determined by v. Békésy may change in their meaning from patient to patient.

A similar test may be carried out with any audiometer. To do this, the intensity variations at the threshold necessary to bring about a disappearance and reappearance of the tone must be determined (Fowler, Hennebert). But such determinations are only to be regarded as crude approximations and are inexact for accurate determination.

Zwislocki and the author (1948*a* and *b*) determine the difference limen by an ordinary audiometer with built-in amplitude modulator calibrated in per cent of the sound pressure. The smallest sound pressure variation which is just perceived as a variation in the loudness is determined, and gives the difference limen. The amplitude modulation may be altered from 0–70%. The changes in intensity set in abruptly. The frequency of the automatic fluctuations is approximately three per second. This gives the smallest difference limen and the most easily determinable. The most suitable intensity for the determination of the difference limen proved to be 40 decibels above threshold, at which value there is little dependence on the frequency and the subject is easily able to notice the fluctuations in the tone (Fig. 1). At and near the threshold, the judgment of the auditory impression is much more difficult

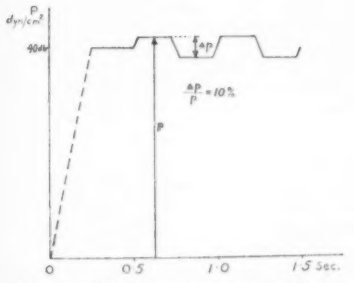


Fig. 1.—Difference limen of sound pressure, i.e. minimum perceptible difference of sound pressure. p reference sound pressure. $\frac{\triangle p}{p}$ absolute difference limen, $\frac{\triangle p}{p}$ relative difference limen.

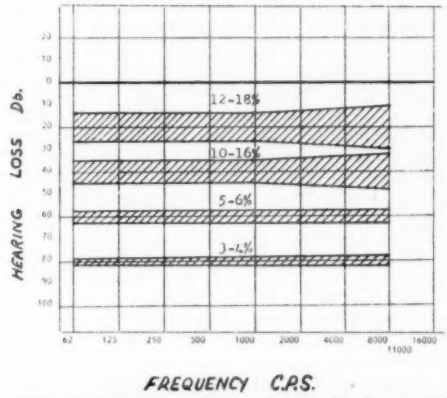


Fig. 2.—Difference limen of intensity in normal hearing. Dependence upon intensity and frequency of the tone. Bands representing the difference limen in per cent. of the sound pressure at different decibels above threshold (Lüscher and Zwislocki).

and the margin of error is relatively greater. Where the degree of deafness does not permit an intensity of 40 decibels above the auditory threshold, the modulation can be carried out at a lower value down to 10 to 15 decibels above the threshold without fundamentally altering the results.

I shall discuss this point later. The greatest degree of accuracy is reached in the middle frequencies from 250–4,000 cycles per second; there is less accuracy below and above, especially near the upper tone limit. It is also easier for the patient to signal the disappearance of the tone variations than their reappearance. Therefore we consider as difference limen the tone intensity variation at which the loudness variation is just no longer perceptible.

As we pointed out in our first papers (1948*a* and *b*) the patients on the whole understand the examination rapidly and are fairly accurate in their responses, although when one does it oneself, one is somewhat unsure in judgment. Unaccountable discrepancies of some of the frequencies may occur and may be due mainly to erroneous judgments of the patients. The margin of error is about $\pm$ 1% of the sound pressure variation. Compared with the maximal difference of the normal values which is 10–16% down to the maximum decrease which is 2–6%, the accuracy is great enough to classify the deafness according to a scheme given later. If threshold audiometry is possible, the determination of the difference limen may almost always be carried out.

On the whole the determination of the difference limen is done in the same way as the threshold audiometry. First the hearing loss curve is taken and afterwards the difference limen for the different frequencies is determined at 40 decibels above threshold. If the deafness is too pronounced to go 40 db. above threshold, the audiometer is set to the maximum intensity which is either 90 or a 100 db. The details of the technique of the determination are discussed at length in our papers (1948*a* and *b*) and by the author and Ermanni (1950). It should be stressed that the technique requires a certain amount of experience and must be learned like any other audiometric examination.

The results can best be represented by recording the difference limen at the corresponding frequencies on the hearing loss curve. A clear method is that of representing the difference limen in per cent by vertical strokes drawn in the curve of the threshold value at points corresponding to the frequencies used. 20 decibels of the audiogram represents a difference limen of 10%. The percentages are marked above the stroke.

The Normal Behaviour of the Difference Limen

The normal behaviour of the difference limen was examined in particular by Riesz (1928, 1933) who found that the number of variations per second depended on the tone intensity and on the frequency. He ascertained that the difference limen is smallest at about three variations per second, decreases rapidly with increasing tone intensity and is greater at the low and high frequencies than at the middle frequencies. Contrary to this relative difference limen, the absolute difference limen increases with increasing tone intensity. The dependency on the frequency is greatest at the threshold and has already practically disappeared at 40 decibels above threshold. We investigated the normal behaviour with our apparatus as far as it was necessary for our determinations. A detailed check of Riesz's results with the electro-acoustic means of to-day seems to be desirable.

Our results confirm that the minimum perceptible difference depends to a very great extent upon the intensity of the tone. Its values fall from 30–50% at 10 decibels above threshold to 2–4% at 80 decibels above threshold (Fig. 2).

The difference limen seems also to depend on the form of tone variation. The determination is much more accurate if the tone variation sets in abruptly than if it is a wave-like variation. In this respect, too, further investigations are necessary. On the other hand, in our determinations the dependency on the frequency at the threshold is much less pronounced than in the results of Riesz. Further investigations are necessary in this direction. The individual variations are rather large, as at 40 decibels above threshold 10–16% is to be regarded as normal. We would even say the normal values go down as far as 8%. We also found fairly often values up to 20%. With increasing experience the difference limen is getting somewhat smaller.

The Difference Limen in Deafness

Investigations into the difference limen were instituted by us some three years ago in the otolaryngological clinic and it has now become so well established and indeed indispensable that its determination occupies a place in the routine examination of all doubtful cases of deafness.

My paper is based therefore on extensive experiences and, in particular, on the careful examination of 71 patients, the results of which have been compiled (Lüscher and Ermanni, 1950).

(*a*) *The difference limen and the recruitment phenomenon.*—The recruitment phenomenon, which was first described by Fowler (1928, 1936, 1937) and by Steinberg and Gardner (1937) is well known. It means a more rapid increase than normal in the subjective loudness when the tone intensity rises, so that in spite of deafness at the threshold, loud tones are perceived as being equally loud as in normal hearing. The recruitment phenomenon is not in evidence in conductive deafness and is characteristic of certain forms of perceptive deafness. Like the difference limen it concerns the relationship between the increase of subjective loudness and the increase of tone intensity and, in theory, it may be concluded that the more rapid increase of subjective loudness presupposes a smaller difference limen. As the increase in subjective loudness occurs most rapidly immediately above the threshold, the phenomenon must be in evidence particularly at the threshold and when the tone intensity is small. When the tone intensity is greater, however, a second factor producing the same effect comes into

play. As I have stressed with regard to the normal behaviour of the difference limen, this becomes smaller with increasing loudness and it is demonstrable that this behaviour holds good for all forms of deafness too. Consequently the difference limen rapidly diminishes as the loudness increases in cases of deafness also; and when the recruitment phenomenon is present it therefore diminishes more rapidly than in the normal ear. There are therefore two factors which lower the difference limen when the recruitment phenomenon is present: on the one hand the more rapid increase in loudness as such, on the other hand the relatively smaller difference limen when the loudness is greater. A summation of the two factors occurs. At the threshold, and immediately above it, the first is most in evidence; as the volume increases the second comes more into play. G. v. Békésy's (1947*a*) method of determining the difference limen at the threshold is based principally on the first; our method (1948*a* and *b*) of determination of the difference limen 40 decibels above the threshold is based primarily on the second.

These theoretical considerations have led to the generally accepted opinion that the recruitment phenomenon and difference limen have the same significance and furthermore that the difference limen may be determined instead of the recruitment phenomenon. So far however there has been no direct proof. I have therefore induced Dr. Neuberger (1950), and the Exchange Assistant of the First Otolaryngological Clinic of Vienna University (Professor Schlander) to verify the relation between the recruitment phenomenon and the difference limen. The examination of 15 patients of different degrees of deafness has made it clear that the two phenomena are parallel. There is not only fundamentally identical behaviour, but also in detail they plot the same curve as shown by Figs. 3, 4 and 5. This furnishes direct

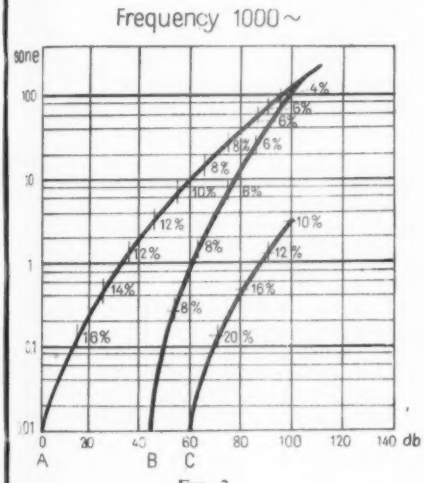


FIG. 3.

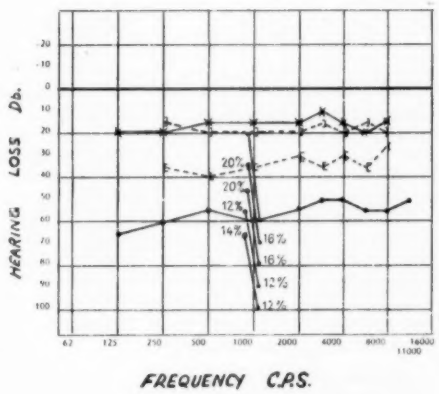


FIG. 4.

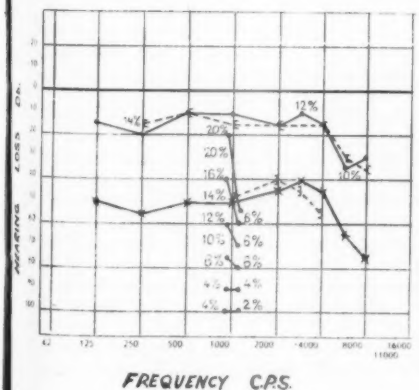


FIG. 5.

FIG. 3.—Recruitment phenomenon and difference limen. Dependence of the difference limen upon the tone intensity and loudness in different types of deafness. A normal hearing, B nervous deafness with recruitment phenomenon, C conductive deafness without recruitment phenomenon (Neuberger).

FIG. 4.—Recruitment phenomenon and difference limen of a unilateral conductive deafness (without recruitment phenomenon). —— air conduction, ---- bone conduction (Neuberger).

FIG. 5.—Recruitment phenomenon and difference limen of a unilateral deafness of the peripheral neural apparatus (with recruitment phenomenon). —— air conduction. ----- bone conduction (Neuberger).

proof that the same significance is to be attached to the difference limen as to the recruitment phenomenon and therefore in cases of binaural deafness the determination of the recruitment phenomenon may be replaced entirely by that of the difference limen. In cases of monaural deafness the determination of the recruitment phenomenon is equivalent to that of the difference limen.

(*b*) *Classification of normal and pathological alterations of the difference limen.*—Almost all forms of deafness produce a decrease of the difference limen, only in psychogenic disturbances do we find an increase. According to our investigations the difference limen can only be described as abnormally low when it sinks below 8% with a loss of hearing of more than 30 decibels in air conduction at 40 decibels above threshold. We have purposely fixed this value lower than the most frequently found normal values of 10–16%.

If the difference limen sinks below 8% it may be assumed that the recruitment phenomenon is present. Between 6 and 8% the difference limen corresponds to a partial recruitment phenomenon; between 2 and 6% it may be assumed that the recruitment phenomenon is present in full. A higher value signifies a slower increase in loudness than is normal: a form of behaviour which has not yet been described in discussions on the recruitment phenomenon. In a certain sense we may speak of its inversion: that is that the difference in loudness between the two ears would become larger as the tone intensity increases. So far we have had no opportunity of verifying this phenomenon directly as we have had no cases of monaural psychogenic hearing disorders.

According to this method of classification it is possible to distinguish between four groups of deafness regarding the difference limen.

TABLE II.—CLASSIFICATION OF THE DIFFERENCE LIMEN IN PER CENT WHERE THERE IS A LOSS OF HEARING OF MORE THAN 30 DECIBELS IN AIR CONDUCTION

Difference in per cent	Relation to the norm	Recruitment phenomenon
More than 16–20	Higher	Increasing loudness difference (?)
8–16	Normal	Absent
6–8	Moderately low	Present in part
2–6	Very low	Present in full

The observations which follow are based upon this way of classification. The method is less exact quantitatively than the determination of threshold values. Loss of hearing of from 10 to 20 decibels is not sufficient to show for certain in the difference limen if recruitment phenomenon is present or not, so that, for example, in mixed deafness the percentage relation of the two components cannot be given accurately. The same applies in a smaller degree to the direct determination of the recruitment phenomenon.

The measurements of the difference limen referred to in the present paper have been carried out by air conduction. It was to be expected that the values determined by bone conduction would be identical, at least in most cases. This was proved by Pirodda, in our laboratory, who compared the difference limen by air and bone conduction directly. He found the same values in normal hearing as well as in different deafnesses, with and without decrease in the difference limen. There may be rare exceptions if the transmission apparatus shows a non-linear distortion.

(*c*) *The difference limen in different forms of deafness.*—The main result of our investigations shows that the various forms of conductive deafness caused by a blockage of the outer auditory canal or by injury or disease of the middle-ear apparatus in the widest sense do not result in an alteration of the difference limen. There is an example given of each: blockage of the auditory canal by ear-defender "Selectone" (Fig. 6), obstruction of the eustachian tube (Fig. 7), mean values of 3 cases of acute (Fig. 8), and 5 cases of chronic inflammation of the middle ear (Fig. 9) and 1 case of an otosclerosis with normal bone conduction (Fig. 10).

This result is in keeping with the general opinion that there is no recruitment phenomenon in cases of conductive deafness.

Conditions are more complicated in deafness which is due to disorders beyond the footplate of the stapes, i.e. in the inner ear, auditory nerve and the central pathways up to the cortex. Here we have every gradation from a normal difference limen to its lowest value.

In this respect, deafness of the inner ear due to acute or chronic acoustic trauma produces characteristic results. In all the cases examined a marked decrease of the difference limen was found. The mean value curve of 14 cases is given in Fig. 11. The mean value in the dip amounted to 5%. An equally characteristic behaviour is exhibited by patients with Ménière's disease in which a pronounced decrease is found. The mean value curve of 6 patients is given in Fig. 12.

The results tally with those of de Bruïne-Altes (1946) and, regarding Ménière's disease, in particular with those of Dix, Hallpike and Hood (1948), who found the recruitment phenomenon always present.

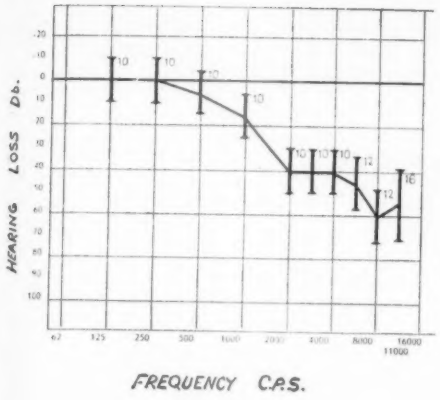


FIG. 6.

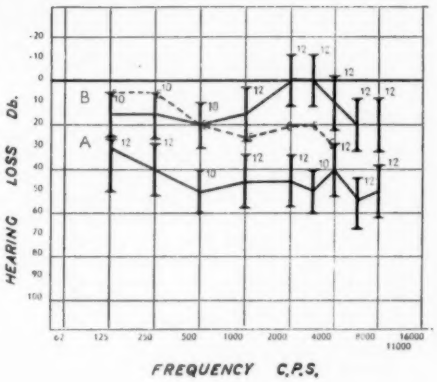


FIG. 7.

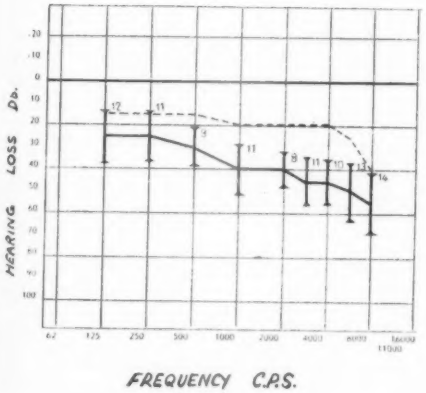


FIG. 8.

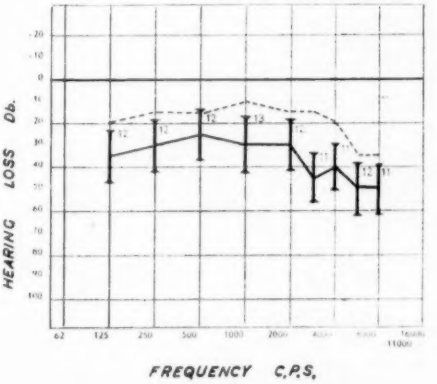


FIG. 9.

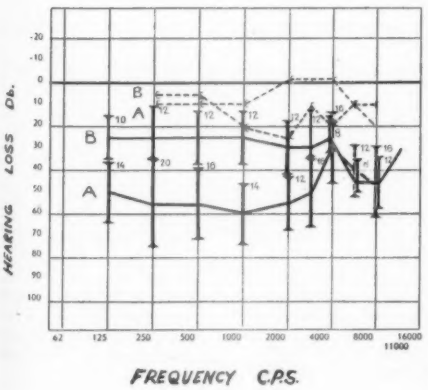


FIG. 10.

FIG. 6.—Difference limen of a blockage of the external meatus by ear-defender "Selectone" (J. Z., male, aged 26, normal hearing). I difference limen in per cent. —— air conduction (Lüscher and Ermanni).

FIG. 7.—Difference limen of a tubal stenosis, (A) before and (B) after catheterization (W. K., aged 21, right ear). I difference limen in per cent. ——air conduction. ----- bone conduction (Lüscher and Ermanni).

FIG. 8.—Mean values of the difference limen in 3 cases of acute otitis media and hearing loss curve. I difference limen in per cent. —— air conduction. ----- bone conduction (Lüscher and Ermanni).

FIG. 9.—Mean values of the difference limen in 5 cases of chronic otitis media and hearing loss curve. I difference limen in per cent. —— air conduction. ----- bone conduction (Lüscher and Ermanni).

FIG. 10.—Difference limen of an otosclerosis with normal bone conduction before (A) and after (B) fenestration (A. G., female, aged 24, right ear). I difference limen in per cent. —— air conduction. ----- bone conduction (Lüscher and Ermanni).

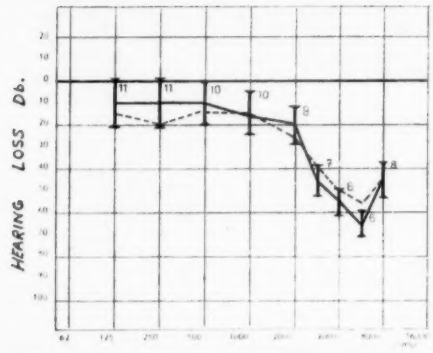


FIG. 11.—Mean values of the difference limen in 14 cases of acoustic trauma and hearing loss curve. I difference limen in per cent. —— air conduction. ----- bone conduction (Lüscher and Ermanni).

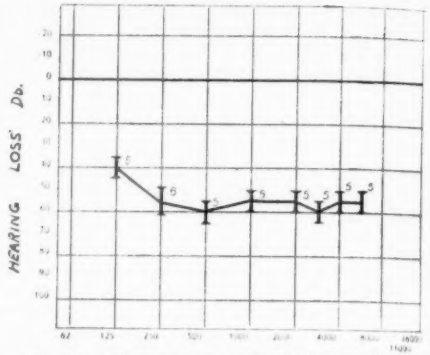


FIG. 12.—Mean values of the difference limen in 6 cases of Ménière's disease and hearing loss curve. I difference limen in per cent. —— air conduction (Lüscher and Ermanni).

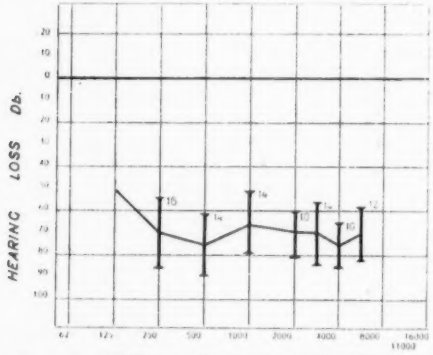


FIG. 13.—Difference limen of a cerebello-pontine tumour (J. W., male, aged 44, left ear). I difference limen in per cent. —— air conduction. Bone conduction not heard (Lüscher and Ermanni).

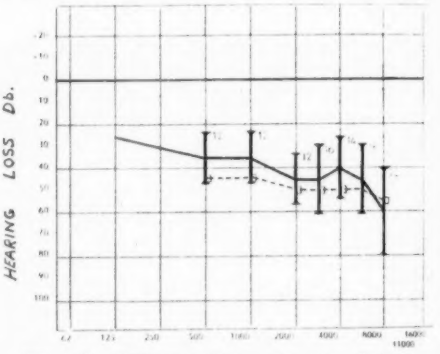
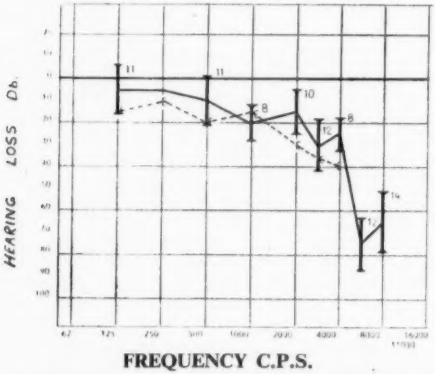
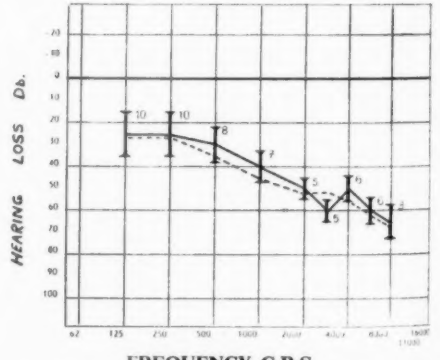


FIG. 14.—Difference limen of a neural deafness after parotitis epidemica (A. R., female, aged 29, left ear). I difference limen in per cent. —— air conduction. ----- bone conduction (Lüscher and Ermanni).



FREQUENCY C.P.S.

FIG. 15.—Difference limen of a (?) central deafness with epileptiform fits and facial tic (A. B., male, aged 69, right ear). I difference limen in per cent. —— air conduction. ----- bone conduction (Lüscher and Ermanni).



FREQUENCY C.P.S.

FIG. 16.—Mean values of the difference limen in 9 cases of "endogenous" deafness of the neural apparatus and hearing loss curve. I difference limen in per cent. —— air conduction. ----- bone conduction (Lüscher and Ermanni).

In contrast to these two groups of deafness with decrease of the difference limen, we have a group with a normal difference limen, viz. retrolabyrinthine hearing disorders. We have been able to observe 5 cases: namely 2 patients with cerebello-pontine tumours, 1 patient with streptomycin damage, a case of deafness due to mumps and a case of deafness probably due to a C.N.S. disorder. As the audiograms, Figs. 13, 14 and 15, demonstrate, the difference limen is normal in every case.

This is consistent with the findings of Dix, Hallpike and Hood (1948) who first demonstrated in 20 cases of acoustic tumours that the recruitment phenomenon was mostly not present and thus showed for the first time that the absence of the recruitment phenomenon is not necessarily confined to conduction deafness, but may also occur in cases of damage to the nervous apparatus. Our own observations go to support the view that such a result is to be obtained not only in cases of acoustic tumours but also in other forms of retrolabyrinthine deafnesses, in various forms of damage to the auditory nerve, the auditory nuclei and probably the central pathways. Our results together with those of Dix, Hallpike and Hood are not in full agreement with those of other authors: for instance Fowler, de Bruïne-Altes.

Between these two forms of deafness each with its clearly defined characteristic behaviour, there is a series of other forms which vary in behaviour from case to case.

In these we must include the so-called endogenous inner ear deafnesses, i.e. hearing disorders which exhibit symptoms of a perceptive deafness without any visible exterior cause. Here we found in most cases (12 out of the 14 patients mentioned) a decrease of the difference limen, but also two exceptions with a normal difference limen to which I shall refer again later. Fig. 16 gives a graph of the mean values of 9 patients with endogenous deafness showing a gradual decrease of the loss of hearing from the low to the high frequencies. The same applies to the components of the inner ear in mixed deafness due to otosclerosis. Discrepancies from the expected diminution of the difference limen are to be found with remarkable frequency in cases of "concussions" of the labyrinth after severe head trauma. Out of 9 patients of this type, Ermanni and the author (1950) found 3 cases with a decrease of 4–7% corresponding to the respective deafness (Fig. 17), 3 cases with a relative diminution from the normally audible to the less perceived frequencies with absolute values of not less than 8% and 3 cases with normal difference limens.

A completely different behaviour is furnished by a probably psychogenic deafness after a trauma caused by an explosion on military service where the difference limen proved to be extremely high: 25–40%, more than two to three times higher than the normal value and four to five times higher than the value expected in nervous deafness (Fig. 18) (Lüscher, 1949).

In another patient with acoustic trauma, probably more or less consciously superimposed psychologically, the same result was observed. Unfortunately we have not had more patients with psychogenic deafness, as these are rather rare in peacetime.

According to a personal communication of Dr. Greiner, Strasbourg, the difference limen is abnormally high in deafness caused by tumours of the temporal lobe.

(*d*) *Difference limen and bone conduction.*—In the foregoing I have indicated various so-called exceptions to the rule in which the difference limen remains normal although the bone conduction is reduced. These cases are of interest, on the one hand with reference to the difference limen, on the other hand with reference to bone conduction.

When bone conduction is normal, the difference limen is normal too. Only in rare exceptions is it diminished: in one case with only slightly impaired bone conduction out of our 71 carefully examined patients (Fig. 19). Steinberg and Gardner (1937) as well as de Bruïne-Altes have also reported exceptional cases of this nature. The condition is mostly found where there is binaural deafness after diseases of the middle ear.

The phenomenon was termed "pseudoregression" by de Bruïne-Altes and still remains unexplained. Steinberg and Gardner suggest a compensation of an impaired bone conduction caused by a conduction disorder, de Bruïne-Altes a non-linear transmission of the sound waves through the middle ear apparatus. In both cases, however, the pseudoregression ought to be most evident at low frequencies, which is not the case.

Reduced bone conduction usually goes with a low difference limen.

As already mentioned, all patients with acoustic trauma have a low difference limen, as have all cases of Ménière's disease and almost all so-called endogenous nerve deafnesses. According to the classical opinion and pathological anatomical findings, these deafnesses are due to a peripheral disorder in the inner ear, i.e. the organ of Corti, acoustic trauma and endogenous deafness especially to a disorder of its nervous apparatus.

It is more rare to find a normal difference limen when bone conduction is bad. It is possible to distinguish between three different pathogenic groups of deafness with this behaviour.

In the first group there is damage to the sound conduction apparatus on the outer side of the stapes footplate, i.e. in the middle ear.

To this group belong patients with acute suppuration of the middle ear (Fig. 20). The discrepancy is also presented in the mean value curve of 5 patients with chronic suppuration

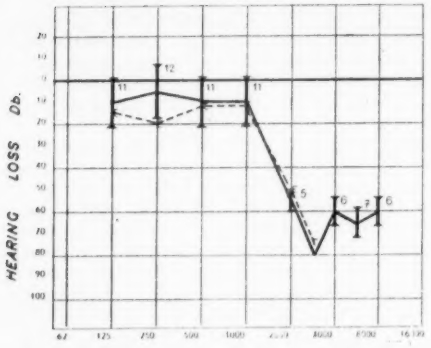


FIG. 17.—Difference limen of a "concussion" of the labyrinth after head trauma (A. F., male, aged 55, right ear). I difference limen. —— air conduction. ----- bone conduction (Lüscher and Ermanni).

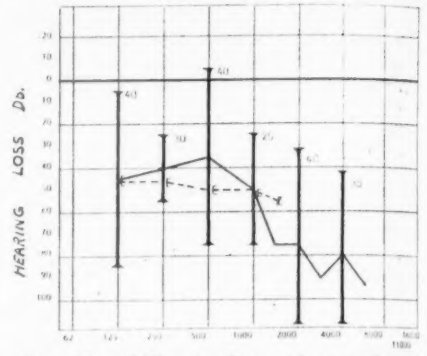


FIG. 18.—Difference limen of a psychogenic deafness (H. S., male, aged 31, left ear). I difference limen. —— air conduction. ----- bone conduction (Lüscher and Ermanni).

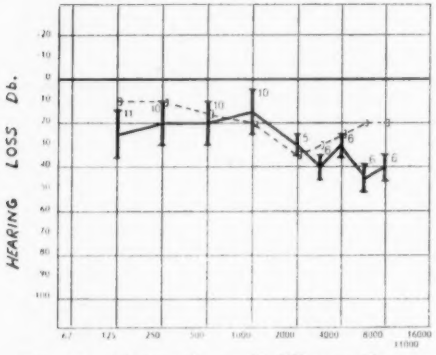


FIG. 19.—Abnormally small difference limen at high frequencies in spite of only slight impaired bone conduction (Pseudoregression) (A. W., female, aged 21, left ear). I difference limen. —— air conduction. ----- bone conduction (Lüscher and Ermanni).

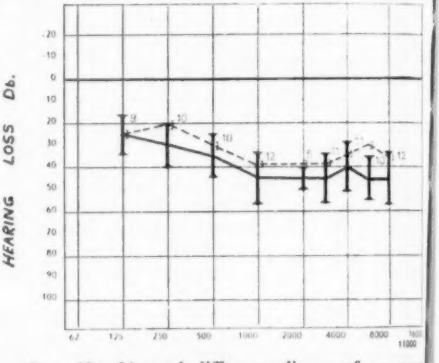


FIG. 20.—Normal difference limen of an acute otitis media with impaired bone conduction (R. Oe. male, aged 36, left ear). I difference limen. —— air conduction. ----- bone conduction (Lüscher and (Ermanni).

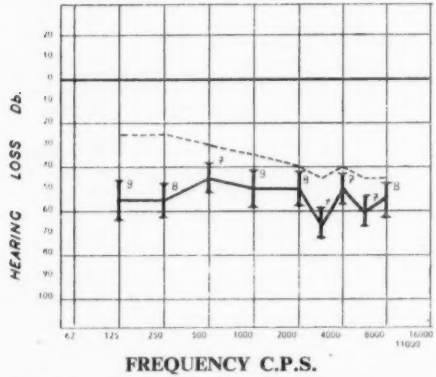


FIG. 21.—Mean values of the difference limen in 5 cases of otosclerosis with mixed deafness and hearing loss curve. I difference limen in per cent. —— air conduction. ----- bone conduction (Lüscher and Ermanni).

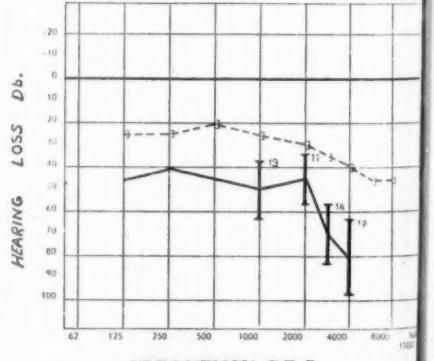


FIG. 22.—Normal difference limen of an ot sclerosis with impaired bone conduction (E. G female, aged 33, left ear). I difference limen —— air conduction. ----- bone conducti (Lüscher and Ermanni).

of the middle ear (Fig. 9). De Bruïne-Altes has also reported an absence of the recruitment phenomenon in one case when the bone conduction was poor. A poor bone conduction in otitis media does not therefore appear always to signify a mixed deafness, i.e. that the nervous apparatus is also involved. The most likely explanation is that the pressure exercised by the suppuration discharge in the middle ear or by the scar formations in chronic inflammation of the middle ear impair the vibrations of not one but both labyrinthine windows and therefore the vibrations of the labyrinthine fluid itself.

Similar conditions are presented by otosclerosis, where in some cases the difference limen gives a normal value in spite of bad bone conduction. Holmgren (1948) has made a similar observation and also de Bruïne-Altes sometimes reported the absence of the recruitment phenomenon. On the whole the difference limen is in accordance with the bone conduction (Fig. 21), which is in keeping with the general experience of poor prognosis for the fenestration in cases of reduced bone conduction. It is quite possible that from time to time a more pronounced impairment of the bone conduction may be caused by a conductive deafness in the inner ear; Holmgren suggests in such cases an obstruction of the fenestra rotunda, but there may also be psychological factors operating, besides unknown factors in the inner ear. Behaviour of this kind is displayed by the patient presented on the audiogram (Fig. 22), where the difference limen is normal or even high, in spite of a pronounced impairment of the bone conduction. Hearing powers were considerably improved by fenestration in respect of air *and* bone conduction, and not only in the operated ear but also in the other. We have reason to believe that psychogenic factors are at work; Shambaugh (1949) is also of the opinion that marked improvement in the other ear is due to such factors.

We cannot decide whether the difference limen is of great importance with regard to prognosis for fenestration, as the number of cases we have been able to observe has been too small. Nevertheless, it is correct to say that a low difference limen suggests a bad prognosis, for in such cases it is certain that the neural apparatus is involved. A normal difference limen on the other hand cannot always be interpreted as favourable.

In a second group of patients with bad bone conduction and normal difference limen signs of a lesion on the outer side of the stapes footplate cannot be detected anamnestically or otoscopically, and a marked decrease in the bone conduction indicates a disorder of the neural apparatus.

To this group belong primarily retrolabyrinthine hearing disorders in which we found a normal difference limen, as mentioned, independently of the seat and type of the disease. The observations of Dix, Hallpike and Hood regarding the absence of the recruitment phenomenon in cases of cerebello-pontine tumours are thus confirmed and amplified. But the number of patients is yet too small to allow us to draw a general conclusion: we can only say that, so far, we have not yet come across a case of retrolabyrinthine damage with a low difference limen.

In addition, there were among 14 endogenous deafnesses the two patients mentioned with bad bone conduction and a normal difference limen.

It was noteworthy that in both cases hereditary factors appeared to be operative and in one case there was also acoustic damage. We know from pathological anatomy that mostly the organ of Corti is damaged in endogenous deafness, but there are also cases with no visible anatomical changes. It is not possible at the present time to give any explanation of this abnormal behaviour. It may be a question of a conductive deafness in the inner ear, which is rather unlikely, or of retrolabyrinthine damage.

A normal difference limen occurs with remarkable frequency in cases of so-called labyrinth "concussion" after severe head trauma characterized by poor bone conduction. This behaviour also is still to be accounted for. A conductive deafness of the labyrinth, perhaps as a result of damage to the basilar membrane or hæmorrhage into the cochlea is to be suspected and in the case of a hæmorrhage even then it would be difficult to explain the form of the audiogram. Retrolabyrinthine damage might be considered too as all the patients had suffered brain concussion, but if this were the case a resemblance between their audiogram and that of patients with acoustic trauma, which is certainly caused by damage to the peripheral receptor, would be astonishing. Psychogenic factors may also play a part, for these patients have often deteriorated considerably and consequently, consciously or unconsciously, they may lack the necessary powers of concentration to perceive the smallest fluctuations of the tone intensity. A low difference limen would be thus compensated for.

A third group with a non-decreased difference limen where the bone conduction is bad is represented by psychogenic deafness—as described before (Lüscher, 1949). The difference limen is on the contrary abnormally high and reaches 30–40%. I have already stressed that

psychological factors might also play a part in certain patients with otosclerosis and in patients who have had accidents. We may indeed ask whether psychogenic hearing disorders, or rather psychogenic superimpositions, are not more frequent than is usually accepted. The numerous psychogenic deafnesses during the war demonstrated that it is very difficult to establish the psychogenic origin of such deafness which usually eludes the normal hearing tests. The surest method at the present time is probably the Doerfler-Stewart (1946) test in which the subject's speech intelligibility is much more impaired by noise than is the case in the normal subject. This is consistent in a certain sense with the increase in the difference limen, i.e. there is an impairment of the ability to distinguish between tone intensities.

The relation of bone conduction to difference limen shows that poor bone conduction does not always indicate a disorder of the neural apparatus, but can obviously be caused also by a pure conductive deafness. Bad bone conduction is not therefore an infallible indication of a disorder in the neural apparatus, a fact which, by the way, has already been established by the Gellé experiment and is suggested by certain audiometric examinations of threshold values. So-called mixed deafnesses can therefore be pure conductive deafnesses. Disorders of the middle-ear apparatus are usually present in those cases. Generally speaking, however, cases of notably poor bone conduction are usually characteristic of lesion of the neural apparatus. In any case conductive deafnesses in the labyrinth which are caused by changes in the cochlea itself, such as stiffening of the basilar membrane, changes in pressure of the perilymph, etc., appear to be rare. According to the latest theories of hearing (Zwislocki (1948) and others), it is understandable that the powers of hearing are relatively independent of changes in the labyrinth apart from changes of viscosity in the labyrinthine fluid or hæmorrhage in the labyrinth. A disorder of this type appears to be present in the temporary deafness after fenestration, whereas the labyrinthine hydrops of Ménière's disease affects the sensory cells. I am not yet in a position to give any information on presbyacusis where transmission deafness of the inner ear is suggested in some cases by the absence of the recruitment phenomenon (de Bruïne-Altes, 1946) and findings of the tone formation (Lüscher and Zwislocki, 1945).

(*e*) *Dependence of the difference limen on frequency.*—I mentioned previously that at 40 decibels above threshold the difference limen is normally independent of the frequency. This is also true of deafnesses with decreased difference limens. In Ménière's disease in particular, an almost horizontally plotted audiogram shows that the difference limen is as small at the lowest tested frequency of 125 cycles per second as at the highest of from 4,000 to 6,000 cycles (*see* Fig. 12). The fact that the recruitment phenomenon is independent of the frequency tallies with this.

(*f*) *Decrease of the difference limen as the tone intensity increases.*—Neuberger (1950) and Ermanni have measured in our laboratory in a series of still unpublished experiments the decrease of the difference limen in different types of poor hearing. In normal hearing and conduction deafnesses there is a fairly gradual decrease as shown in Figs. 3, 4 and 5.

In deafnesses where the recruitment phenomenon is present, the greater the degree of deafness, the more quickly the decrease usually takes place. In cases of deafness of more than 70 decibels hearing loss, the decrease in the difference limen is usually very marked at 10 decibels above the threshold and often reaches values of less than 8% so that in these cases, as already mentioned, the difference limen may be examined and evaluated at less than 40 decibels without being converted. In these cases the patient experiences no difficulty in giving his difference limen immediately above the threshold, whereas in normal hearing or in conduction deafnesses the uncertainty immediately above the threshold is relatively great.

Topical Diagnostic Significance of the Difference Limen

According to theoretical considerations and as Neuberger has now demonstrated directly, the recruitment phenomenon and the difference limen are identical in behaviour and may be regarded as manifestations of one and the same fundamental phenomenon. Their topical diagnostic significance is thus identical. Until the findings of Dix, Hallpike and Hood concerning acoustic tumours, the presence of the recruitment phenomenon was generally accepted as a sure proof of a disorder of the neural apparatus, whereas its absence was taken to indicate a conductive deafness. The recruitment phenomenon was thus considered to be a reliable means of distinguishing between conductive deafnesses and disorders of the neural apparatus. This assumption, however, is shown by the investigations of Dix, Hallpike and Hood as well as by our own findings not to be true under all conditions. It is true that a decrease in the difference limen, i.e. the presence of the recruitment phenomenon, proves that damage has been caused to the neural apparatus of the ear. Very rare exceptions to this rule are found in pseudoregressions. On the other hand a normal difference limen cannot be taken as a certain proof of a conductive deafness, as a normal difference limen is met with in retrolabyrinthine deafnesses and is found to be even larger than normal in psychogenic hearing disorders.

Consequently the decrease in the difference limen does not always indicate a disorder of the neural apparatus but characterizes peripheral damage to the sound receptor, i.e. the organ of Corti and appears to be in evidence when the sensory cells are damaged. The topical diagnostic significance of the difference limen is, however, not diminished by this, for it enables us to pick out of the large group of neural deafnesses, disorders of the organ of Corti. Furthermore, it is probable that psychogenic hearing disorders are characterized by an increase in the difference limen, so that our topical diagnosis can thus enable us to single out two types of deafness in the neural apparatus. In addition a third group, the retrolabyrinthine deafnesses with normal difference limen, may be determined if poor bone conduction is taken into consideration. As I already pointed out a certain reservation is to be made regarding the retrolabyrinthine deafnesses. If there is no retrolabyrinthine disorder, the difference limen enables us to distinguish between a conductive deafness and a disorder of the neural apparatus (Table III).

TABLE III.—DIAGNOSTIC SIGNIFICANCE OF DIFFERENCE LIMEN AND RECRUITMENT PHENOMENON

Type of deafness	Difference limen	Recruitment phenomenon
(1) Conductive deafness	normal	absent
(2) Disorders of the neural apparatus		
(*a*) Peripheral receptor (sensory cells) ..	low	present
(*b*) Retrolabyrinthine deafnesses ..	normal	absent
(*c*) Psychogenic deafness (Cortex?) ..	high	?

As for the general distinction between conductive deafnesses and disorders of the neural apparatus, it is possible that fatigue tests will be substituted for the difference limen, for according to all the evidence so far available concerning fatigue in different forms of deafness, all disorders of the neural apparatus appear to be accompanied by an increased rate of fatigue.

In conclusion space does not permit me to go into the various explanatory hypotheses concerning the recruitment phenomenon and difference limen, I have had to give so many facts that theory has had to be neglected. In a later paper we shall put forward views in this connexion and discuss the various explanations of Lurie (1940), Dix, Hallpike and Hood (1948), Tumarkin (1950) and others.

SUMMARY

(1) The present paper is based upon the determination of the difference limen for tone intensity variations by the Lüscher-Zwislocki method and is a report on experiences in the Basle otolaryngological clinic and policlinic.

(2) The normal difference limen is dependent to a very great extent upon the tone intensity; it decreases rapidly as the tone intensity increases. At 10 decibels above threshold it amounts to 30–50%, at 80 decibels to 2–4% of the reference sound pressure.

(3) A direct comparison of the difference limen and the recruitment phenomenon shows that the two phenomena are parallel and that the more pronounced the recruitment phenomenon is, the smaller is the difference limen. The difference limen is related to the recruitment phenomenon in two ways: (*a*) by the more rapid increase of loudness as such; (*b*) by the decrease of the difference limen as the tone intensity increases. The first phenomenon is in evidence mainly at the threshold, the second at greater tone intensities.

(4) Distinction is made between a high difference limen (more than 16–20% of the basic sound pressure), normal (8–16%), moderately low (6–8%) and very low (4–6%). These values correspond to a tone intensity of 40 decibels above threshold and a hearing loss of 30 decibels or more in air conduction.

(5) Conductive deafnesses due to alterations in the external meatus or middle ear, such as obstruction of the auditory meatus or of the eustachian tube, acute or chronic otitis media and otosclerosis with normal bone conduction have a normal difference limen.

(6) Perceptive deafnesses are less uniform in their behaviour. The difference limen is usually diminished.

(7) A marked decrease of the difference limen was in evidence in all the cases of acoustic trauma the author examined, and also in all patients with Ménière's disease.

(8) On the other hand the difference limen proved normal in 5 patients with retrolabyrinthine hearing disorders (1 acoustic tumour, 1 cerebello-pontine tumour, 1 streptomycin damage, 1 parotitis epidemica, 1 central hearing disorder).

(9) In cases of endogenous labyrinthine deafnesses, the difference limen is usually decreased, but normal values may be met with.

(10) Patients with "concussion" of the labyrinth after severe head trauma are not uniform in their behaviour. Out of 9 patients of this type, 3 had a decrease of the difference limen corresponding to the deafness, 3 had only a relative diminution at less perceived frequencies and 3 had normal values.

(11) 2 patients with psychogenic hearing disorders exhibited a high difference limen of 20–40%.

(12) With rare exceptions, normal bone conduction is accompanied by a normal difference limen.

(13) A reduction in bone conduction generally means a decrease of the difference limen. There are, however, three groups of exceptions: (1) disease of the middle ear as an expression of conductive deafness with bad bone conduction; (2) in retrolabyrinthine hearing disorders, seldom in endogenous labyrinthine deafness, somewhat more frequently in "concussion" of the inner ear after severe head trauma; (3) in psychogenic deafness with a high difference limen.

(14) Conductive deafnesses in the labyrinth as a consequence of changes in the labyrinth itself seem to be rare.

(15) The decrease of the difference limen is not dependent on the frequency.

(16) The greater the deafness is, the more rapidly the decrease in the difference limen occurs when the tone intensity increases, in so far as it is a deafness with a decrease in the difference limen, i.e. with recruitment phenomenon.

(17) The difference limen and the recruitment phenomenon may be regarded from the topical diagnostic point of view as being equivalent.

(18) The difference limen appears to be dependent on the function of the peripheral receptor, i.e. the sensory cells. An impairment of the difference limen indicates damage to the organ of Corti and thus allows peripheral disorders of the neural apparatus to be recognized. According to our experiences so far, the difference limen permits us to divide disorders of the neural apparatus into three groups: (1) disorders of the peripheral receptor, i.e. the sensory cells of the organ of Corti with decrease in the difference limen; (2) retrolabyrinth organic hearing disorders with normal difference limen; (3) psychogenic hearing disorders with a high difference limen. In so far as a retrolabyrinthine and psychogenic hearing disorder may be excluded, it permits a distinction to be made between conductive deafness and disorders of the neural apparatus.

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Auditory Adaptation and Its Relationship to Clinical Tests of Auditory Function

By J. D. Hood, Ph.D.

It has been known for many years that fatigue or loss of sensitivity results from prolonged auditory stimulation. The study of this phenomenon has been confined for the most part to the measurement of the elevation of the threshold of hearing *following* the application of a stimulus, and for this reason we have found it convenient to term it Post-stimulatory Fatigue.

Fig. 1 illustrates the method which we have used for studying the phenomenon. It consists essentially of an audiometer and recording mechanism.

The apparatus was devised by Dr. Hallpike and Dr. Schuster in 1942 for studying the effects of blast waves upon the cochlea, and we have found it very useful.

The attenuator control of the audiometer is coupled directly by means of a rack and pinion mechanism to an ink recorder. The attenuation in decibels is proportioned to the angle of rotation of the control and the amplitude of the resulting trace is thus proportional to the intensity change in decibels of the sound.

The apparatus has been applied in our fatigue tests and in Fig. 2 is shown a typical test result.

The subject first executes the threshold tracing seen on the left of the figure. This he does by rotating the attenuator control in a rhythmical manner in the neighbourhood of his threshold of hearing. The amplitude of the excursions is normally some 2 to 6 decibels with a time interval between successive peaks of about 2 to 3 seconds. The peaks of the tracing give the just heard level.

In the case illustrated the intensity is raised at the end of one minute to 100 db. above threshold for a period of one minute. The subject then again traces his threshold. It will be seen that fatigue, as measured by the displacement of the threshold level, is still present two minutes after the cessation of the stimulus.

This brings us to the consideration of the measurement of a sensitivity loss of a different kind, and one which manifests itself only during the application of the stimulus. We have accordingly termed it Per-stimulatory Fatigue.

The equipment described has lent itself well to the demonstration and study of this phenomenon, and Fig. 3 is intended to show the test procedure.

On the subject's right there is, as before, the audiometer and threshold recorder; on his left, an additional audiometer. Each audiometer supplies a separate ear-piece, and it is possible by means of an appropriate switching arrangement to stimulate either or both ears. The two audiometers are first adjusted to the same frequency, say 1,000 cycles. The intensity at one ear, the subject's left, is kept constant, say at 80 db. above threshold. The intensity at the right ear is then varied using the threshold recorder to give equality of loudness with the constant tone in the left ear.

Fig. 4 shows the result of such a test procedure.

At the start loudness equality is attained with an intensity in the subject's right or control ear, as it may be called, which is the same as that of the left or test ear, i.e. 80 db. The next step is to switch off the variable tone from the right ear and continue the constant stimulus in the left ear. After a period which may be determined at will, the variable tone is reapplied to the right ear, and it is then found that a loudness balance is attained with an intensity in the right ear which is less than 80 db. by an amount which may be considerable and depends within certain limits upon the duration of application of the constant stimulus.

It will be seen, therefore, that during the period of this application a loss of sensitivity or fatigue of the left or test ear has occurred which is measured by this change, 30 db. in the level at the control ear required to give this final loudness balance.

It will be seen from Fig. 5 that the amount of the fatigue varies with the intensity of the fatiguing tone.

This also shows that irrespective of its amount, the fatigue attains a maximum after a period which has a constant value of about three and a half minutes.

The next point of importance is the recovery process of this fatigue, and this is depicted in Fig. 6.

As before, the first operation is to make the usual loudness balance, in this case at 80 db. at 1,000 cycles. The control ear is then rested while the test ear is fatigued for at least three minutes. At the end of this period the fatigue has reached a level of 30 db. At this point both ears are rested for periods varying from a few seconds to one minute. At the end of each rest period, the fatiguing tone is applied at 80 db. as before, to the test ear, while simultaneously the variable tone is reapplied to the control ear with resumption of the balancing procedure. The diagram shows the different stages of recovery after four different rest periods 0, 10, 30 and 60 seconds.

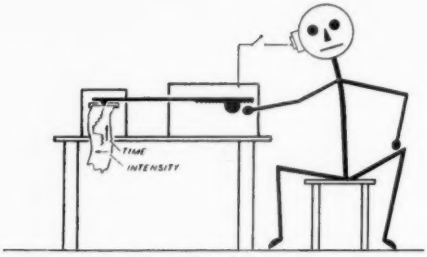


FIG. 1.

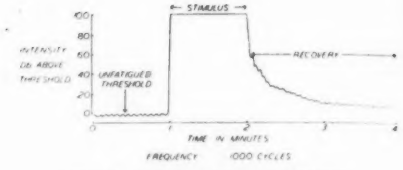


FIG. 2.—Post-stimulatory fatigue.

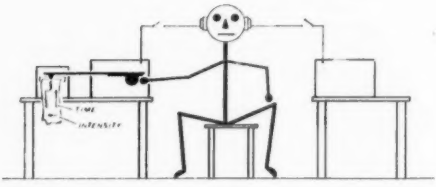


FIG. 3.

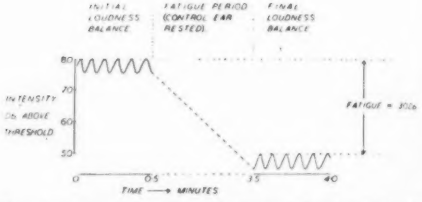


FIG. 4.—Per-stimulatory fatigue. Stimulus intensity 80 db. Frequency 1,000 cycles.

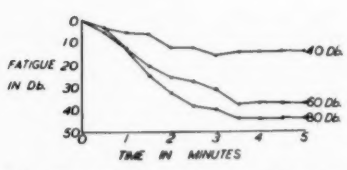


FIG. 5.—Per-stimulatory fatigue: Development. Stimulus frequency 1,000 cycles.

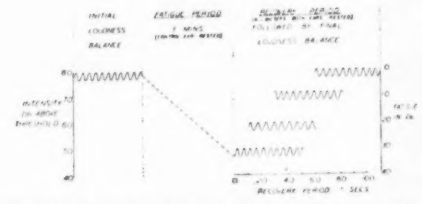


FIG. 6.—Per-stimulatory fatigue: Recovery. Stimulus intensity 80 db. Frequency 1,000 cycles.

FIG. 7.

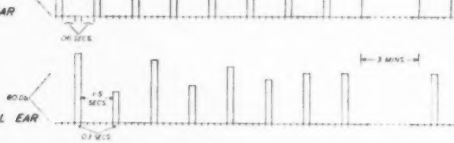


FIG. 8.

It will be seen that recovery is most rapid during the first ten seconds, but that fatigue is still present but much reduced up to one minute after the cessation of the fatiguing tone.

We come now to the consideration of another and better known binaural loudness balancing procedure, known as the alternate balance procedure, and one which is in common use in the investigation of auditory function. Here a balance is made by listening to tones presented to each ear alternately, a procedure which would seem well suited to the measurement of fatigue. We have attempted to use it for this purpose, and a diagrammatic representation of the test procedure is shown in Fig. 7.

The subject wears a pair of telephone receivers with which short-tone impulses are delivered alternately to the test ear and the control ear. The frequency used in this case was 1,000 cycles. The intensity at the test ear is 80 db. with a final loudness matching at 80 db. at the control ear.

The transfer of the stimulus from one ear to the other is carried out with a change-over switch which is operated in a rhythmical manner, and is found by measurement to give the time relations shown in the diagram. The duration of each impulse was about 0·3 second. The switch was in the off position for about 0·6 second, giving an interval between successive stimuli to the same ear of 1·5 seconds.

Following the attainment of the loudness balance, the test ear is fatigued continuously for three minutes. Thereafter further loudness comparisons are made and the balance at 80 db. in each ear is found to be unchanged. In fact, no fatigue is demonstrable.

Now it is the particular purpose of this communication to draw attention to the striking difference between the results obtained with these two procedures, the simultaneous and alternate balance.

In both, the same fatiguing stimulus has been applied. While, however, considerable fatigue can be readily demonstrated with the simultaneous balance test, the alternate balance test reveals none at all. This striking difference appears to depend upon certain important time constants of the nervous apparatus of the cochlea, in particular upon the difference in the manner of their involvement under the conditions of the two test procedures. Here, Matthew's investigation of adaptation of single muscle end-organs appears (1931) to be particularly significant.

His results are represented diagrammatically in Fig. 8. When a stimulus is applied to an end-organ the action potential response consists of an initial high frequency discharge known as the on-effect. The duration of this initial burst of impulses is brief, being of the order of 0·2 second, and is followed by a slow decline in the discharge frequency with time. This decline is termed adaptation.

If, following adaptation, the stimulus is removed and then reapplied after a rest period greater than about one second, the on-effect is present and indeed undiminished, but continued stimulation results in a rapid relapse of the response, i.e. an accelerated, adaptation to a level which is determined by the duration of the rest period. If, however, the rest period is less than 0·2 second no on-effect is present, while for durations of rest period between 0·2 and 1 second the on-effect is present but diminished.

Let us consider how these time constants can be applied to the interpretation of our observations. It would seem likely that, following the application of the fatiguing tone and its momentary interruption, the loudness level attained on reapplication might temporarily relapse with abnormal rapidity, as shown in Fig. 8, to the fatigued level. Nevertheless, the subjective measure of the loudness for the short-tone stimuli used in the alternate balance technique might depend upon the on-effects alone. The magnitude of these is unreduced, and thus no fatigue would be manifest.

This interpretation has been applied to the results obtained with both the simultaneous and alternate balancing techniques, and the results are embodied in Fig. 9.

The upper two diagrams explain the apparent absence of fatigue when investigated by the alternate balance procedure. The lower two explain the presence of per-stimulatory fatigue demonstrable by the simultaneous balancing technique.

The tones are of equal intensity and are applied to the ears of a normal subject. The diagrams show the supposed variations in magnitude of the total action potential responses which constitute the physiological basis of our subjective observations.

In the initial balance period A is shown a series of pulses in the two ears, all of the same magnitude corresponding to equality of loudness. In the second period B, a continuous fatiguing tone is applied to the test ear, and its response declines in the manner shown. In the third period C, we revert to the alternating pulses and, since the on-effect in the fatigued ear is unimpaired, the magnitude of the pulses is equal in the two ears corresponding again to equality of loudness. Below is shown the course of events with the simultaneous balancing procedure. In the initial balancing period A, the responses from the two ears decline in exactly the same way. In periods B and C we see how the continued application of the test tone causes a progressive decline in the response. Meanwhile, during period B the control ear is rested.

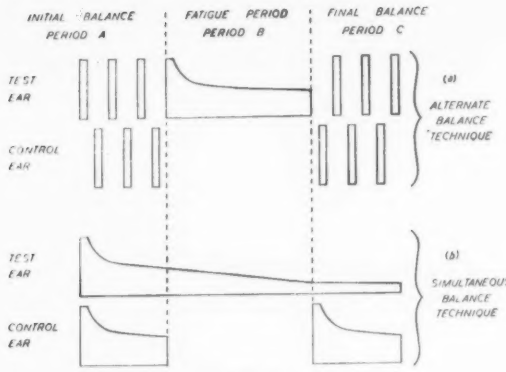


FIG. 9.

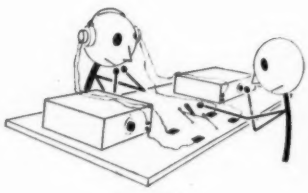


FIG. 10.

The tone is reapplied to the control ear in the final balancing period C and the response, being that of a normal unadapted set of sense organs, is of correspondingly high magnitude, and exceeds that of the test ear.

The subjective response from the test ear at this stage of the procedure is therefore one of diminished loudness, as exhibited in our experiments.

It would seem possible in this way to give a satisfactory explanation of the striking difference in the results obtained by the two balancing techniques, the alternate balance and the simultaneous balance. This difference is an important one for the illustration it gives of the need for designing and interpreting subjective tests of cochlear function in the light of the fundamental physiological factors concerned.

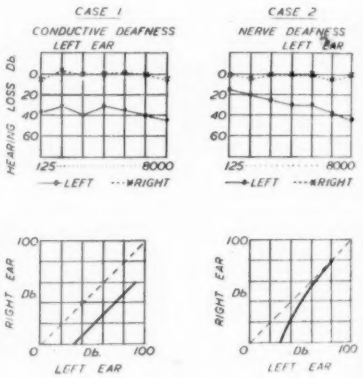


FIG. 11.

This point arises with particular force in connexion with another and particularly useful clinical test of cochlear function, namely the Loudness Recruitment test. This test was first described by E. P. Fowler, and it formed the basis of a communication given by Dix, Hallpike, and Hood to the Royal Society of Medicine (1948).

Our own investigations on so-called per-stimulatory fatigue seem to throw some light upon this phenomenon, and it is necessary to digress a little at this point to review very briefly the characteristics of the phenomenon and the usual test procedure used for its demonstration. This is shown in Fig. 10.

The subject wears a pair of telephone receivers, each supplied by a separate pure tone audiometer, or preferably by a single audiometer with arrangements for independent adjustment of the intensity in the two receivers. The frequency of the sound stimulus is the same in each receiver, and the tester switches it alternately from right to left.

The audiograms of two typical cases of unilateral deafness are shown in Fig. 11. In Case 1 the deafness is due to a lesion of the conducting mechanism of the left middle ear, and in Case 2 to Ménière's disease affecting the left labyrinth.

The purpose of the test is to equate a tone of variable intensity in the impaired ear with a tone of constant intensity in the normal ear. The constant tone is altered in increasing steps of 20 decibels after each loudness balance has been achieved and the results are plotted conventionally on a graph of the form shown (Fig. 11).

The ordinates represent the intensity of the constant tone in the normal ear and the abscissa, the sound intensities in the impaired ear, giving equality of loudness. In the case of a normal subject, loudness equality is, of course, attained with equal intensities in the two ears giving the dotted 45 degree line shown in the diagram. In both cases shown, the test frequency was 1,000 cycles, at which point the audiogram shows a threshold shift for the affected ear of 30 db., and this is denoted on the chart by the lowest point of the curve in each case. In the case of conductive deafness the obstruction caused by the middle-ear disease to the sound

waves on their way to the inner ear introduces an attenuation factor, in this case 30 db., which is constant at all intensities. The result, therefore, is a curve inclined at the same angle as that of the normal, but displaced to the right by 30 decibels.

In Case 2 the audiogram is essentially the same as in Case 1, with a threshold shift of 30 db. at 1,000 cycles per sec.

On ascending the intensity scale, however, it is found that the sensitivity loss or deafness of the left ear, 30 db. at threshold, becomes progressively less until at 80 db. equal intensities at the two ears evoke equal loudness responses.

In other words, the deafness of the affected ear present at threshold disappears at higher intensities, and this in its simplest terms constitutes the phenomenon of loudness recruitment.

One further point arises. It will be seen that in Case 2, the whole loudness range of the test is, in the normal ear, covered by an intensity range of 80 db., while the same loudness range in the impaired ear is covered by only 50 db. Thus equal *intensity* increments are attended by much greater *loudness* increments in the impaired than in the normal ear. Conversely, for equal increment of *loudness* much smaller increments of *intensity* are needed in the impaired than in the normal ear. It follows from this that diminution of the difference limen, which Lüscher (1950) has studied in such detail, is a natural and indeed inevitable corollary of loudness recruitment as it is assessed by the balancing technique which Fowler (1936) originally described and which we have used. It can in fact be said that loudness recruitment and diminution of the difference limen are both manifestations of the same essential disorder of cochlear function.

It will be observed that we have arrived at this result using the second of the two loudness balancing techniques described earlier, namely the alternate binaural loudness balancing technique. From this we are led to certain conclusions of very great importance. We see in the first place that under the conditions of this test the loudness comparisons are dependent only on the on-effects in the two ears.

Now if the conclusions of Hallpike (1948, 1938) on the pathology of Ménière's disease be accepted, namely that the endolymph distension is accompanied by disease of the hair cells of Corti's organ, then it follows from our own findings that these diseased hair cells are capable of exhibiting on-effects of normal magnitude.

Now, as explained earlier, the first of the loudness balancing techniques, namely the simultaneous balancing technique, involves a comparison not of the initial responses, that is, the on-effects, from the two ears, but of their sustained responses to continued stimuli, in fact the adapted responses. It was therefore thought worth while to investigate these adapted responses in monaural deafness due to Ménière's disease and conductive lesions by means of the simultaneous balancing technique and, in particular, to ascertain whether or not the loudness recruitment phenomenon, present in the on-effect with Ménière's disease could also be demonstrated in the adapted response.

Let us consider again and in rather greater detail the simultaneous balancing procedure in the case of normal subjects. In Fig. 12 are two tracings taken in this way.

They represent the intensity variations in one ear, the control ear, required for equality of loudness with a constant tone, in this case 80 db., at 1,000 cycles; in the other ear, shown on the right; in each case taken over a period of five minutes. As would be expected, the 80 db. test tone is matched by a tone of equal intensity in the control ear. The point of importance is that the level of the tracings remains very constant over the five minutes. In other words, any fatigue brought about by the constant 80 db. stimulus in the test ear is matched by equal fatigue brought about by the varying stimulus in the control ear.

In Fig. 13 is shown the course of events with the same balancing procedure at 1,000 cycles applied to unilateral *conductive* deafness.

The deafness at threshold is 30 db. The diagrams on the right represent the constant intensities applied to the impaired or test ear, i.e. 40, 60 and 80 db. above normal threshold. Those on the left show the actual balance tracings obtained from the normal ear at each of these three levels.

It will be seen that for a constant tone of 40 db. in the impaired ear, equality of loudness is obtained as would be expected with a tone of 10 db. in the normal ear. Similarly with a tone of 60 db. in the impaired ear, loudness equality is obtained with a tone of 30 db. in the normal ear, and with 80 db. in the impaired ear 50 db. in the normal ear. In other words, as in the case of the alternate balancing technique applied to unilateral conductive deafness, so with the simultaneous balancing technique, the loudness of the sound in the impaired ear is reduced at each of the three intensity levels by the same attenuation factor, 30 db. Apart from this fact the tracings are identical with those obtained from normal subjects.

The results obtained in a case of unilateral end-organ deafness (Ménière's disease) are shown in Fig. 14.

As before, the threshold loss was 30 db. and on the right will be seen once again the same constant intensities applied to the impaired ear. We will consider first the balance tracing from the normal ear with a constant tone of 40 db. applied to the impaired ear.

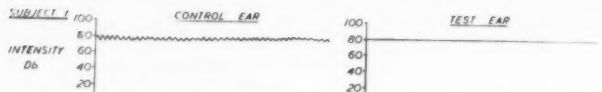


FIG. 12.

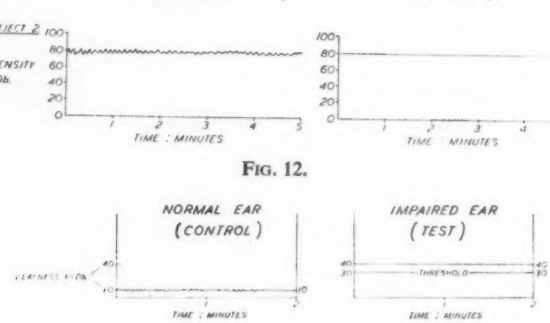


FIG. 13.

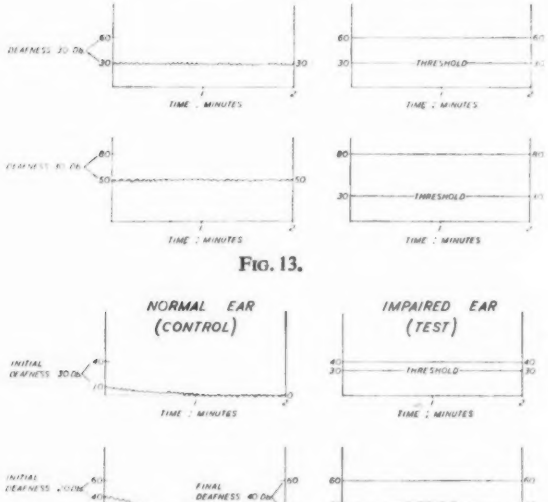


FIG. 14.

As can be seen, equality of loudness is first obtained with a tone of 10 db. in the control ear. As the test proceeds, however, this intensity falls until eventually it approaches the threshold level. Now since this tracing from the control ear is a measure of the loudness of the tone in the impaired ear, it would seem that the constant 40 db. stimulus, although still being applied to the impaired ear, was no longer being heard.

When we consider the second pair of diagrams, we see that with a stimulus intensity of 60 db. applied to the impaired ear, loudness equality is initially obtained with an intensity of 40 db. in the control ear. That is to say, the 30 db. loss at threshold has been reduced on account of recruitment to one of 20 db. With continued stimulation, however, the tracing

falls very rapidly, and the final balancing intensity is only 20 db. In other words, the loudness level of the constant tone in the impaired ear was at first high, 40 db., on account of recruitment; but it soon falls and reaches this new level of 20 db. This means that the deafness of 30 db. is first temporarily reduced by recruitment. Thereafter the recruitment seems to disappear and we are left instead with an actual increase of the deafness to 40 db.

In the case of the third pair of diagrams, the stimulus intensity applied to the impaired ear is 80 db. and the initial balancing intensity 70 db. There is thus almost complete recruitment of loudness. The final balancing level, however, is 30 db. so that the deafness of the impaired ear, after being temporarily reduced to 10 db. by recruitment, is finally increased to 50 db.

We have examined 20 cases of unilateral Ménière's disease, and obtained similar results in all. The final balancing intensity, as can be seen, is not so precise and definite as in the case of the conventional alternate balancing procedure, but falls progressively with time. In general, nevertheless, the fall does reach a maximal decline and thereafter remains constant, and it is this final intensity that we have established in all cases and used as a measure of the loudness loss.

The results for two characteristic subjects are shown in Fig. 15 together with the results obtained with the alternate balancing procedure.

It will be seen, that whereas recruitment *is* present with the one, it is *not* with the other. Instead, in Case 2, we obtain a state of affairs which is, perhaps, best described as recruitment reversion.

Clearly the phenomenon of loudness recruitment is a transient one and in some ways a false indication of cochlear function.

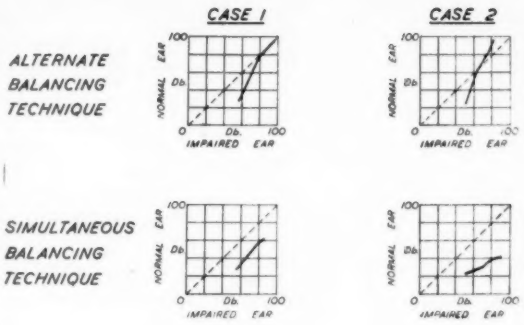


FIG. 15.

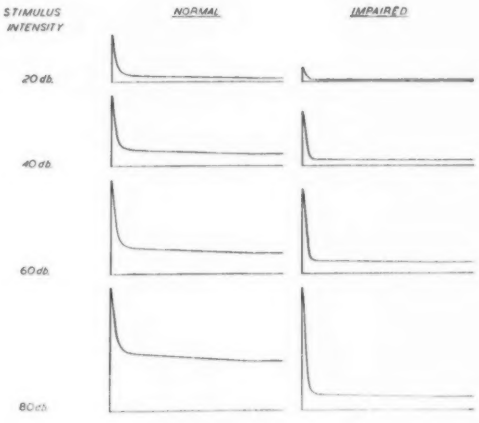


FIG. 16.

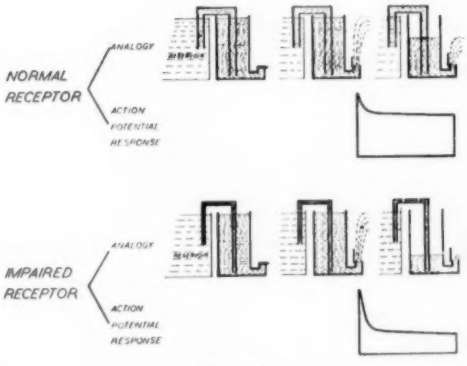


FIG. 17.

We have applied once more our interpretation of what we suppose to be the neural response from both normal and impaired ears, and the results are shown in Fig. 16.

Here are shown the supposed action potential responses from the normal and impaired ears, corresponding to different stimulus intensities.

For a 20 db. stimulus the on-effect in the normal ear is small, and in the impaired ear it is still smaller, corresponding to the deafness at low stimulus intensities. As the intensities are raised the on-effects in the impaired ear approach the size of the corresponding on-effects from the normal ear. At 80 db. they are equal, corresponding to complete recruitment.

The responses from the impaired ear to sustained stimuli, however, are shown to be much reduced from those of the normal ear, corresponding to the results obtained with the simultaneous balancing procedure, namely recruitment reversion.

To sum up then, we can say that recruitment of loudness in a case of end-organ deafness is mediated by a recruitment in the magnitude of the on-effects. The neural response, however, to a sustained stimulus is marked by an abnormally great adaptation, and it is this to which we must attribute the abnormally great decline of loudness which is demonstrable with the simultaneous loudness balancing technique.

Adaptation is generally regarded as a process of equilibration whereby the energy dissipated by the end-organ is matched by an equal restoration of energy. The capacity of a receptor to respond to a sustained stimulus is dictated therefore by the rate at which fresh energy can be supplied to it.

It would seem that in the case of end-organ deafness this capacity of the receptors is grossly impaired and the response consequently falls considerably below that of the normal.

This process has a simple analogy in the discharge and replenishment of a water tank, as shown in Fig. 17.

The upper set of tanks represents a normal receptor; the lower set an impaired receptor. The capacity of each is the same, but the supply pipe to the lower tank is of much smaller diameter than that to the upper tank. The first tank in each case represents the quiescent condition of the two receptors, and it will be seen that they are identical, i.e. the height of the water level in each is the same.

When the taps are opened, corresponding to the response of the respective receptor to a stimulus, the initial fountains are of equal height as in the case of the two on-effects. In time, the water level in the two tanks falls to a level at which a state of equilibrium exists between the in-flow and the out-flow of the water. This is the condition of the adapted receptor when the energy supplied just balances the energy dissipated. Since the supply to the lower tank is reduced, the equilibrium water level is low and the height of the fountain much reduced, corresponding to the adapted level of the action potential response of the impaired receptor. In other words, the energy reserve is deficient.

We consider this finding to be an important one. In the first place because the measurement of the degree of adaptation may prove of some diagnostic value as an assessment of the true physiological impairment of function of the cochlear end-organs and in the second place because it would seem likely to be, at any rate, one of the reasons why recruitment of loudness is not accompanied by recruitment of intelligibility.

In recapitulation it may be said that our own investigations and those of Lüscher and Zwislocki (1948) have now made it clear that the loudness recruitment phenomenon depends upon disordered function of the hair cells resulting from disease or injury. Although their response is absent or reduced when the stimulus level is low, nevertheless their initial response (on-effect) may approximate to or even exceed the normal if the stimulus level is high. But this response is not sustained if the stimulus is continued, and indeed it may show an abnormal tendency to relapse, a characteristic which again seems likely to be the result of hair cell disease. These facts must be taken into account in the design of test procedures for the investigation of the phenomenon. This means, in essence, that the duration and spacing of the stimuli should be so arranged as to involve only the on-effects. Thus, the duration of the interval between successive stimuli to one ear should in all probability have a value not less than one second, while the duration of each stimulus should be sufficient to produce a sensation of tone. It need not, in all probability, much exceed this.

Within these limits the phenomenon can as well be investigated by the alternate binaural balancing procedure described by Fowler as by the differential threshold method of Lüscher and Zwislocki. But any technique which involves sustained stimulation is likely to bring into play the pathological adaptation of the sustained response, which as we have shown, is also a characteristic of hair cell disease and may lead, as we have described, to elimination or even reversal of the recruitment.

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